DAC/Petition
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#26

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Kyorin Pharmaceutical Company, Ltd.
U.S. Patent No.: U.S. Patent No. 4,980,470
Issue Date: December 25, 1990
For: 8-Alkoxyquinolonecarboxylic Acid and Salts Thereof
Inventors: Kuniyoshi Masuzawa, Seigo Suzue, Keiji Hirai and Takayoshi Ishizaki

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Your Applicant, Kyorin Pharmaceutical Company, Ltd., a corporation organized and existing under the laws of Japan and having offices at 5, Kanda Surugadai 2-chome, Chiyoda-ku, Tokyo, Japan represents that it is the assignee of the entire interest in and to Letters Patent of the United States Patent No. 4,980,470 ('470 Patent) granted to Kuniyoshi Masuzawa, Seigo Suzue, Keiji Hirai and Takayoshi Ishizaki on the 25th day of December 1990 for 8-Alkoxyquinolonecarboxylic Acid and Salts Thereof. Your Applicant, acting through its duly authorized Agent, Bristol-Myers Squibb Company, a corporation of the State of Delaware and the undersigned attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the guidelines and rules published by the U.S. Patent and Trademark Office. An originally executed Authorization of Agent and Power of Attorney evidencing the appointment of Bristol-Myers Squibb Company and the undersigned as duly appointed Agent is attached hereto as "Exhibit 1".

As a result of an Agreement dated September 30, 1996 with Kyorin Pharmaceutical Company, Ltd., Bristol-Myers Squibb Company is the Licensee of the exclusive rights to the '470 patent, having the exclusive license to make, use and sell the compound (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid, an antibacterial agent also known as gatifloxacin, claimed in said patent throughout the United States for the full and true term of the '470 patent. In conjunction with its exclusive license under the '470 patent, Bristol-Myers Squibb Company at a cost of many millions of dollars has undertaken through its United States Pharmaceutical Research Institute the commercial development of gatifloxacin over the past several years including the performance of extensive clinical trials pursuant to an Investigational New Drug Application ("IND") and the ultimate filing of a New Drug Application ("NDA") in order to obtain approval by the U.S. Food and Drug Administration ("FDA") for the commercial marketing of gatifloxacin. On December 17, 1999, the FDA granted approval of Bristol-Myers Squibb's NDA on the use of gatifloxacin for the treatment of a variety of bacterial infections. This FDA approval consituted the first permitted commercial marketing or use of gatifloxacin.

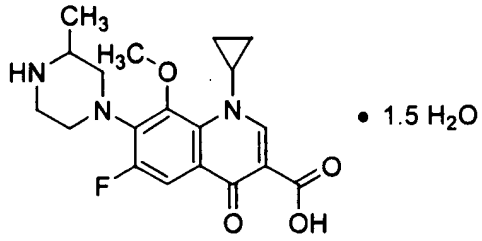
Based on these IND and NDA regulatory review periods and in accordance with the provisions of 35 U.S.C. §156, Kyorin Pharamaceutical Company, Ltd. with the approval and consent of Bristol-Myers Squibb Company, the holder of the regulatory approval granted with respect to the IND and NDA regulatory review periods, is hereby seeking the requested extension of the '470 patent for 720 days, from December 25, 2007 to and including December 14, 2009.

SECTION 1

Complete Identification of the Approved Product

The approved product, which is known generically as gatifloxacin and which will be marketed by Bristol-Myers Squibb Company under the tradename TEQUIN, has:

The structural formula



a) The empirical formula $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$

b) A molecular weight of 402.42

c) The chemical name: (±)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate

The package insert for TEQUIN is attached hereto as "Exhibit 2".

SECTION 2

Complete identification of the Federal Statute including the applicable provision of law under which the regulation occurred.

Pursuant to Section 505 (c)(1)(A) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. 355(c)(1)(A] NDA #21-061 was approved and received permission for commercial marketing on December 17, 1999. The regulatory review period began on December 26, 1996 relative to the medical indication of TEQUIN as an oral antibacterial agent, i.e. 30 days after receipt by the FDA of IND # 52,081. A chronology of the regulatory review period is provided in Sections 11 and 12.

SECTION 3

Identification of the date on which the product received permission for commercial marketing

NDA #21-061 was approved on December 17, 1999 pursuant to Section 505(c) of the Federal Food, Drug and Cosmetic Act.

SECTION 4

Identification of each active ingredient in the product

Gatifloxacin is the only active ingredient of the approved product and has not been previously approved for commercial marketing or use.

SECTION 5

This application is being submitted within the sixty(60) day period pursuant to 37 CFR 1,720(f) since FDA approval was granted on December 17, 1999 and the sixty day period will lapse on February 15, 2000.

SECTION 6

Complete identification of the patent

The patent for which extension is sought is U.S. Patent 4,980,470 which was issued on December 25, 1990 and set to expire on December 25, 2007. The patent is based on U.S. Patent Application No. 3,822 filed by Kuniyoshi Masuzawa, Seigo Suzue, Keiji Hirai and Takayoshi Ishizaki on January 16, 1987. The patent is owned by Kyorin Pharmaceutical Company, Ltd. by virtue of an assignment from the inventors. The pertinent assignment was recorded on November 23, 1988 in the United States Patent and Trademark Office at Reel 4983, Frame 330 and 331.

SECTION 7

A copy of U.S. Patent No. 4,980,470 which is entitled 8-ALKOXYQUINOLONECARBOXYLIC ACID AND SALTS THEREOF is provided as "Exhibit 3".

SECTION 8

A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment or reexamination certificate issued in the patent

A copy of a Certificate of Correction dated August 11, 1992 is provided as "Exhibit 4".

Copies of the receipts for the first and second maintenace fee payments are provided as "Exhibit 5" and "Exhibit 6".

SECTION 9

Statement that the patent claims the approved product

U.S. Patent No. 4,980,470 claims gatifloxacin, the active ingredient in TEQUIN.

Claim 1 of U.S. Patent No. 4,980,470 generically claims gatifloxacin, i.e. when R = a hydrogen atom, R^1 is methyl, a lower alkyl group, R^2 = a hydrogen atom, X = fluorine, a halogen atom and Z = 3-methylpiperazino.

Claim 4 of U.S. Patent No. 4,980,470 covers gatifloxacin (claimed specifically by chemical name).

SECTION 10

Relevant dates and information pursuant to 35 U.S.C. 156(g) to enable a determination of the applicable regulatory review period

December 26, 1996	Effective date of Notice of claimed Investigational Exemption (IND) For use of TEQUIN as an oral antibacterial agent (IND # 52,081)
December 28, 1998	Date of submission of New Drug Application # 21-061 for TEQUIN to the U.S. FDA.
December 17, 1999	NDA approval date

SECTION 11

Brief description of the activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and significant dates applicable to such activities

Bristol-Myers Squibb Company which through an Agreement dated September 30, 1996 is the exclusive licensee of the compound gatifloxacin, undertook the development of TEQUIN to establish by adequate and well-controlled clinical trials its safety and effectiveness as an antibacterial agent. Since the product was a new drug as defined under Section 201(P) of the Federal Food, Drug and Cosmetic Act, an appproved NDA for the product was required to be obtained under Section 505(b) of said Act prior to its commercial marketing.

The following is a brief description of certain significant activities undertaken by Bristol-Myers Squibb Company during the applicable regulatory review period with respect to TEQUIN including the dates applicable to such activities. Continuing from the date of the first use in humans through the time of FDA approval, there were clinical studies in progress and/or being planned, with regular and frequent communications between Bristol-Myers Squibb Company and its clinical investigators.

November 26, 1996	Investigational New Drug Application # 52,081 for Gatifloxacin for Oral Use was filed. This provided for initial clinical studies under Protocols AI420-003 (pneumonia) and AI420-004 (bronchitis).
December 26, 1996	Effective date of IND #52,081.
January 8, 1997	Communication from FDA that clinical studies for gatifloxacin may commence.
January 20, 1997	Submission of Protocol AI420-006 (atypical pneumonia).
January 30, 1997	Submission of Protocol AI420-007 (sinusitis).
February 1, 1997	The first use in humans in the United States.
March 25, 1997	Submission of Protocol AI420-020 (bronchitis).
April 2, 1997	Submission of Protocol AI420-002 (pneumonia).

April 8, 1997	Submission of Protocol AI420-010 (uncomplicated urinary tract infections).
April 28, 1997	Submission of Protocol AI420-011 (complicated urinary tract infections).
May 21, 1997	Submission of Protocol AI420-012 (gonnorhea) and Protocol AI420-031 (complicated urinary tract infections).
June 13, 1997	Submission of Protocol AI420-005 (uncomplicated skin and soft tissue infections).
June 23, 1997	Investigational New Drug Application #53,521 for Gatifloxacin for Intravenous Use was filed.
July 8, 1997	Submission of Protocol AI420-001 (bronchitis).
July 14, 1997	Submission of Protocol AI420-008 (sinusitis).
July 24, 1997	Discussion with FDA on Protocols AI420-002, AI420-003, AI420-005, and AI420-006.
August 15, 1997	"End of Phase II" meeting is held with FDA to discuss further clinical development of gatifloxacin.
August 27, 1997	Submission of Protocol AI420-037 (pneumonia) and Protocol AI420-038 (pneumonia). Discussion with FDA on Protocols AI420-001, AI420-004, AI420-007, AI420-008, AI420-020.
September 10, 1997	Discussion with FDA on Protocols AI420-010, AI420-011, AI420-012, and AI420-031.
October 7, 1997	"End of Phase II" meeting with FDA chemists on issues involving chemistry, manufacturing, and controls. Discussion with FDA on Protocols AI420-037, AI420-038.
February 6, 1998	Submission of Analysis Plan for Study AI420-010.
March 3, 1998	Submission of Annual IND Report.
March 12, 1998	Submission of Analysis Plan for Study AI420-004.
April 3, 1998	"Pre-NDA" meeting is held to discuss content and format of proposed New Drug Applications (NDA) for TEQUIN™ (gatifloxacin) Tablets and TEQUIN™ (gatifloxacin) Injection.

April 13, 1998	Submission of Analysis Plans for Studies AI420-011 and AI420-031.
April 20, 1998	Submission of Analysis Plan for Study AI420-012.
June 10, 1998	Submission of Analysis Plan for Study AI420-005.
June 19, 1998	Submission of Analysis Plans for Studies AI420-001, AI420-002, AI420-006, AI420-007, AI420-008, AI420-020, AI420-037, AI420-038.
June 26, 1998	Submission of Analysis Plan for Study AI420-003.
July 7, 1998	Discussion with FDA on Analysis Plans for Studies AI420-005, AI420-011, AI420-012, AI420-031.
August 7, 1998	Discussion with FDA on Analysis Plans for Studies AI420-001, AI420-002, AI420-003, AI420-006, AI420-007, AI420-008, AI420-020, AI420-038, AI420-038.
August 26, 1998	Submission of Format for Integrated Summary of Safety and Efficacy is submitted.
September 2, 1998	Meeting with FDA on Electronic Submission plans for NDA and software demonstration.
September 14,1998	Submission of Protocols AI420-061 (pneumonia), -062 (pneumonia), -064 (bronchitis) and –066 (sinusitis).
October 1,1998	Submission of Sample SAS version 5 transport file for AI420-004 as test of electronic data transfer.
October 2, 1998	Submission of draft protocol AI420-063.
October 28, 1998	Discussion with FDA on randomization techniques in clinical trials.
December 21,1998	Submission of Final Study Reports for AI420-004, -017, -037, and –038.

NDA Activities

December 28,1998	Submission of Initial New Drug Application
January 21, 1999	Submission of a proposal on statistical approach to evaluate confidence intervals in clinical trials (in response to an FDA request)
January 27, 1999	Response to FDA Chemistry Reviewer's questions
February 3, 1999	Discussion with FDA on fileability of sinusitis indication
March 12, 1999	Submission of responses to FDA request for the top five enrolling sites in comparative, pivotal studies AI420-002, -005, -011, and –012.
March 18,1999	Proposal for 4-Month Safety Update Report filed
March 19, 1999	Submission to FDA of Patent Information Declaration
March 31,1999	Submission of responses to FDA request regarding Test of cure windows in studies AI420-002 and -008
April 16, 1999	Submission of response to FDA request for criterion for sputum purulence in study AI420-001
May 5, 1999	Submission of 4-Month Safety Update
May 10, 1999	Response to FDA request for information and Microbiology data
June 8, 1999	Submission of electronic clinical pharmacology data files
June 10, 1999	Discussion with FDA review of sinusitis indication
June 16,1999	Response to request for CMC information addressing sterilization of IV product
July 1, 1999	Response to request for microbiology report and core data package sent to NCCLS to assist microbiology review at FDA
July 12, 1999	Response to request for Final Study Report of AI420-007
August 12, 1999	Response to request for additional clinical data
August 19, 1999	Response to request for additional information on patients in AI420-003, -006, -037 and –038

September 1,1999	Discussion with FDA of liver function test tables
September 3, 1999	Response to request for additional analysis of liver function test data
September 7, 1999	Discussion with FDA on Clinical Pharmacology/Biopharmaceutics review
September 24, 1999	Submission of a proposed Package Insert
October 6, 1999	Teleconference to discuss Labeling
October 22, 1999	Submission of revised proposed Package Insert
October 29, 1999	Submission of revised proposed Package Insert
November 2, 1999	Discussion with FDA on Pediatric clinical trials
November 9, 1999	Discussion with FDA on toxicology section of Package Insert
November 18, 1999	Discussion with FDA regarding otitis media studies
November 29, 1999	Discussion with FDA on Pharmacokinetics section of Package Insert
December 2, 1999	Discussion with FDA on Microbiology issues and Clinical Indications
December 8, 1999	Discussion with FDA on Safety sections of the Package Insert
December 17, 1999	FDA approval of NDA

SECTION 12

Patent extension eligibility and the length of extension claimed.

U.S. Patent No. 4,980,470 is eligible for an extension of 720 days based on the following:

(a) The '470 patent claims the composition of matter, gatifloxacin, both generically (Claim 1) and specifically (Claim 4), which is the active ingredient of the approved human drug product, TEQUIN;

(b) The term of said patent has never been previously extended;

(c) The application for extension of patent term is submitted by the owner of the patent, Kyorin Pharmaceutical Ltd.;

(d) The product, TEQUIN, has been subject to regulatory review prior to commercial marketing or use;

(e) The product received permission for commercial marketing on December 17, 1999 and the application for patent term extension has been submitted within 60 days from that date;

(f) No other patent term has been extended for the same regulatory review period for this product.

The length of extension claimed was determined in accordance with 35 USC §156(g) and 37 CFR §1.775(d). Since the subject patent, United States Patent No. 4,980,470, was issued after the 1984 enactment of §156 and the clinical investigation under IND #52,081 also commenced after the 1984 enactment date, the period of extension based on the regulatory review may not exceed five years, nor may the patent be extended beyond fourteen years after the NDA approval date.

The total extension time comprises the sum total of the testing and approval periods, less one-half of the days in the testing period. In the present case, the pertinent dates are:

Patent issued:	December 25, 1990
Testing period began:	December 26, 1996
NDA submitted:	December 28, 1998
NDA approved	December 17, 1999

Calculation of the total extension time pursuant to 37 CFR §1.775(d)(4) yields 720 days according to the formula:

1086 (number of days from IND to approval of NDA) – 366 (one-half the number of days from IND to submission of the NDA)

The above-calculated extension time is not affected by the limitations in 37 CFR § 1.775 in that addition of 14 years to the NDA approval date would lead to a date of December 17, 2013 and the addition of five years to the original expiration date of the paten would lead to a date of December 25, 2012, both dates being beyond the requested expiration date (with extension) of December 14, 2009.

SECTION 13

Duty of Disclosure

The applicant, Kyorin Pharmaceutical Company, Ltd. hereby acknowledges its duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to this application for patent term extension.

SECTION 14

Prescribed Fee

Authorization in accordance with 37 CFR §1.20(j) is given to charge the One Thousand and Sixty Dollar ($1060.00) fee for receiving and acting upon the application for extension to Deposit Account No. 02.3850. In the event the actual fee differs from this amount, it is requested that the overpayment or underpayment be credited or charged to Deposit Account No. 02.3850.

SECTION 15

Inquiries and Correspondence:

Inquiries and correspondence relating to this Application for Patent Term Extension of the '470 patent should be directed to

David M. Morse,
Patent Counsel – Wallingford
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492
Telephone: (203)677-6997

SECTION 16

Duplicate Application Paper

A duplicate of this Application for Patent Term Extension of the '470 patent hereby certified, as such, is being submitted herewith.

SECTION 17

Oath or declaration

The following declaration of David M. Morse is submitted herewith in compliance with the requirements of 37 CFR § 1.740(b):

The undersigned acting pursuant to an Authorization of Agent and Power of Attorney executed by Kyorin Pharmaceutical Company, Ltd., the applicant submitting this Application for Patent Term Extension of United States Patent No. 4,980,470 hereinabove referred to as the '470 patent, in compliance with the requirements of 37 CFR §1.740(b)(1), hereby avers as follows:

1. He is a patent attorney authorized to practice before the United States Patent and Trademark Office (Reg. No. 25,742) and pursuant to an Authorization of Agent and Power of Attorney from Kyorin Pharmaceutical Company, Ltd., the assignee of record of the "470 patent, a copy of which is attached as Exhibit 1, he is authorized to represent Kyorin Pharmaceutical Company, Ltd. in this application for Patent Term Extension of the '470 patent and to transact all business in the United States Patent and Trademark Office in connection therewith;

2. He has reviewed and understands the contents of this Application for Patent Term Extension of the'470 patent;

3. He believes that the '470 patent is subject to patent term extension pursuant to the provision of 37 CFR §1.710;

4. He believes that the extension of the length claimed in this Application for Patent Term Extension of the '470 patent is justified under 35 USC §156 and the applicable regulations relating thereto;

5. He believes that the '470 patent which is the subject of this Application for Patent Term Extension meets the conditions for patent term extension as set forth in 37 CFR §1.720; and

6. He declares that all of the statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this patent extension and any extension of U.S. Patent No. 4,980,470.

Respectfully submitted,

KYORIN PHARMACEUTICAL COMPANY, LTD.

By David M. Morse

David M. Morse, Esq.
Registration No. 25,742
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660
Phone: (203) 677-6997

Dated: Feb. 11, 2000

February 11, 2000

Enclosures

Exhibit 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kyorin Pharmaceutical Company, Ltd.
U.S. Patent No.:	U.S. Patent No. 4,980,470
Issue Date:	December 25, 1990
For:	8-Alkoxyquinolonecarboxylic Acid and Salts Thereof
Inventors:	Kuniyoshi Masuzawa, Seigo Suzue, Keiji Hirai and Takayoshi Ishizaki

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

AUTHORIZATION OF AGENT AND POWER OF ATTORNEY

Kyorin Pharmaceutical Company, Ltd., a corporation organized and existing under the laws of Japan and having offices at 5, Kanda Surugadai 2-chome, Chiyoda-ku, Tokyo, Japan, being the owner of record of the above-identified U.S. Letters Patent, hereby authorize and appoint, Bristol-Myers Squibb Company, a corporation organized and existing under the laws of the State of Delaware and having its principal office at 345 Park Avenue, New York, New York 10154, and the Patent Attorneys/Agents named below:

David M. Morse	Registration No. 25,742
Samuel J. DuBoff	Registration No. 25,969
Richard P. Ryan	Registration No. 30,491
Aldo A. Algieri	Registration No. 31,697

all being employees of Bristol-Myers Squibb Company, individually and collectively to be the agents and attorneys of Kyorin Pharmaceutical Company, Ltd. with regard to an application for extension of the term of U.S. Patent No. 4,980,470 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please address all communciations in the above matter to:

David M. Morse
Patent Counsel – Wallingford
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

KYORIN PHARMACEUTICAL COMPANY, LTD.

By: _____

Name: Ikuo Ogihara

Title: President

Respectfully submitted,

_____

David M. Morse, Esq.
Registration No. 25,742
Bristol-Myers Squibb Company
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660
Phone: (203) 677-6997

Date: Feb. 11, 2000

Bristol-Myers Squibb

Rx only

TEQUIN™ Tablets
(gatifloxacin)
TEQUIN™ Injection
(gatifloxacin)

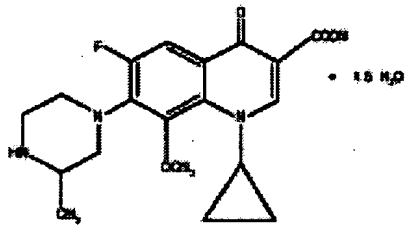
(Patient Information Included)

TEQUIN™ is available as TEQUIN (gatifloxacin) Tablets for oral administration and as TEQUIN (gatifloxacin) Injection for intravenous administration.

DESCRIPTION

TEQUIN contains gatifloxacin, a synthetic broad-spectrum 8-methoxyfluoroquinolone antibacterial agent for oral or intravenous administration. Chemically, gatifloxacin is (±) -1-cyclopropyl-6-fluoro-1, 4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate.

The chemical structure is:



Its empirical formula is $C_{19}H_{22}FN_3O_4 \cdot 1.5\ H_2O$ and its molecular weight is 402.42. Gatifloxacin is a sesquihydrate crystalline powder and is white to pale yellow in color. It exists as a racemate, with no net optical rotation. The solubility of the compound is pH dependent. The maximum aqueous solubility (40-60 mg/mL) occurs at a pH range of 2 to 5.

TEQUIN Tablets

TEQUIN Tablets are available as 200-mg and 400-mg white, film-coated tablets and contain the following inactive ingredients: hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, simethicone, sodium starch glycolate, sorbic acid, and titanium dioxide.

TEQUIN Injection

TEQUIN Injection is available in 20-mL (200-mg) and 40-mL (400-mg) single-use vials as a sterile, preservative-free aqueous solution of gatifloxacin with pH ranging from 3.5 to 5.5. TEQUIN Injection is also available in ready-to-use 100-mL (200-mg) and 200-mL (400-mg) flexible bags as a sterile, preservative-free aqueous solution of gatifloxacin with pH ranging from 3.5 to 5.5. The appearance of the intravenous solution may range from light yellow to greenish-yellow in color. The color does not affect nor is it indicative of product stability.

The intravenous formulation contains dextrose, anhydrous, USP or dextrose, monohydrate, USP and Water for Injection, USP, and may contain hydrochloric acid and/or sodium hydroxide for pH adjustment.

CLINICAL PHARMACOLOGY

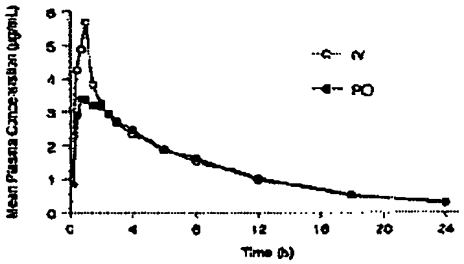
Gatifloxacin is administered as a racemate, with the disposition and antibacterial activity of the R- and S-enantiomers virtually identical.

Absorption

Gatifloxacin is well absorbed from the gastrointestinal tract after oral administration and can be given without regard to food. The absolute bioavailability of gatifloxacin is 96%. Peak plasma concentrations of gatifloxacin usually occur 1-2 hours after oral dosing.

The oral and intravenous routes of administration for TEQUIN can be considered interchangeable, since the pharmacokinetics of gatifloxacin after 1-hour intravenous administration are similar to those observed for orally administered gatifloxacin when equal doses are administered (Figure 1) (see **DOSAGE AND ADMINISTRATION**).

Figure 1. Mean Plasma Concentration-Time Profiles of Gatifloxacin Following Intravenous (IV) and Oral (PO) Administration of a Single 400-mg Dose to Healthy Subjects.



Pharmacokinetics

The mean (SD) pharmacokinetic parameters of gatifloxacin following oral administration to healthy subjects with bacterial infections and subjects with renal insufficiency are listed in Table 1. The mean (SD) pharmacokinetic parameters of gatifloxacin following intravenous administration to healthy subjects are listed in Table 2.

Table 1
Gatifloxacin Pharmacokinetic Parameters – Oral Administration

	C_{max} (µg/mL)	T_{max}[a] (h)	AUC[b] (µg•h/mL)	$T_{1/2}$ (h)	Cl/F (mL/min)	Cl_R (mL/min)	UR (%)
200 mg – Healthy Volunteers							
Single dose (n=12)	2.0 ± 0.4	1.00 (0.50, 2.50)	14.2 ± 0.4	–	241 ± 40	–	73.8 ± 10.9
400 mg – Healthy Volunteers							
Single dose (n=202)[c]	3.8 ± 1.0	1.00 (0.50, 6.00)	33.0 ± 6.2	7.8 ± 1.3	210 ± 44	151 ± 46	72.4 ± 18.1
Multiple dose (n=18)	4.2 ± 1.3	1.00 (0.50, 4.00)	34.4 ± 5.7	7.1 ± 0.6	199 ± 31	159 ± 34	80.2 ± 12.1
400 mg – Patients with Infection							
Multiple dose (n=140)[d]	4.2 ± 1.9	–	51.3 ± 20.4	–	147 ± 48	–	–
400 mg – Single Dose Subjects with Renal Insufficiency							
Cl_{cr} 50 - 89 mL/min (n=8)	4.4 ± 1.1	1.13 (0.75-2.00)	48.0 ± 12.7	11.2 ± 2.8	148 ± 41	124 ± 38	83.7 ± 7.8
Cl_{cr} 30 - 49 mL/min (n=8)	5.1 ± 1.8	0.75 (0.50, 6.00)	74.9 ± 12.6	17.2 ± 8.5	92 ± 17	67 ± 24	71.1 ± 17.4
Cl_{cr} <30 mL/min (n=8)	4.5 ± 1.2	1.50 (0.50, 6.00)	149.3 ± 35.6	30.7 ± 8.4	48 ± 16	23 ± 13	44.7 ± 13.0
Hemodialysis (n=8)	4.7 ± 1.0	1.50 (1.00, 3.00)	180.3 ± 34.4	35.7 ± 7.0	38 ± 8	–	–
CAPD (n=8)	4.7 ± 1.3	1.75 (0.50, 3.00)	227.0 ± 60.0	40.3 ± 8.3	31 ± 8	–	–

[a] Median (Minimum, Maximum)
[b] Single dose: AUC (0-∞), Multiple dose: AUC (0-24)
[c] n=184 for Cl/F, n=134 for Cl_R, and n=132 for UR;
[d] Based on the patient population pharmacokinetic modeling, n=103 for C_{max}
C_{max}: Maximum serum concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Cl/F: Apparent total clearance; Cl_R: Renal clearance; UR: Urinary recovery.

Table 2
Gatifloxacin Pharmacokinetic Parameters – Intravenous Administration

	C_{max} (μg/mL)	T_{max}[a] (h)	AUC[b] (μg•h/mL)	$T_{1/2}$ (h)	Vd_{ss} (L/kg)	Cl (mL/min)	Cl_R (mL/min)	UR (%)
200 mg – Healthy Volunteers								
Single dose (n=12)	2.2 ± 0.3	1.00 (0.67, 1.50)	15.9 ± 2.6	11.1 ± 4.1	1.9 ± 0.1	214 ± 36	155 ± 32	71.7 ± 6.8
Multiple dose (n=8)[c]	2.4 ± 0.4	1.00 (0.67, 1.00)	16.8 ± 3.6	12.3 ± 4.6	2.0 ± 0.3	207 ± 44	155 ± 55	72.4 ± 16.4
400 mg – Healthy Volunteers								
Single dose (n=30)	5.5 ± 1.0	1.00 (0.50, 1.00)	35.1 ± 6.7	7.4 ± 1.6	1.5 ± 0.2	196 ± 33	124 ± 41	62.3 ± 16.7
Multiple dose (n=5)	4.6 ± 0.6	1.00 (1.00, 1.00)	35.4 ± 4.6	13.9 ± 3.9	1.6 ± 0.5	190 ± 24	161 ± 43	83.5 ± 13.8

[a] Median (Minimum, Maximum)
[b] Single dose: AUC (0-∞), Multiple dose: AUC (0-24)
[c] n=7 for Cl_R and UR
C_{max}: Maximum serum concentration; T_{max}: Time to C_{max}; AUC: Area under concentration versus time curve; $T_{1/2}$: Serum half-life; Vd_{ss}: Volume of distribution; Cl: Total clearance; Cl_R: Renal clearance; UR: Urinary recovery.

Gatifloxacin pharmacokinetics are linear and time-independent at doses ranging from 200 to 800 mg administered over a period of up to 14 days. Steady-state concentrations are achieved by the third daily oral or intravenous dose of gatifloxacin. The mean steady-state peak and trough plasma concentrations attained following a dosing regimen of 400 mg once daily are approximately 4.2 μg/mL and 0.4 μg/mL, respectively, for oral administration and 4.6 μg/mL and 0.4 μg/mL, respectively, for intravenous administration.

Distribution

Serum protein binding of gatifloxacin is approximately 20% in volunteers and is concentration independent. Consistent with the low protein binding, concentrations of gatifloxacin in saliva were approximately equal to those in plasma (mean [range] saliva:plasma ratio was 0.88 [0.46-1.57]). The mean volume of distribution of gatifloxacin at steady-state (Vd_{SS}) ranged from 1.5 to 2.0 L/kg. Gatifloxacin is widely distributed throughout the body into many body tissues and fluids. Rapid distribution of gatifloxacin into tissues results in higher gatifloxacin concentrations in most target tissues than in serum (Table 3).

Table 3
Gatifloxacin Tissue-Fluid/Serum Ratio (Range)[a]

Fluid or Tissue	Tissue-Fluid/Serum Ratio (Range)[a]
Respiratory	
Alveolar macrophages	26.5 (10.9-61.1)
Bronchial mucosa	1.65 (1.12-2.22)
Lung epithelial lining fluid	1.67 (0.81-4.46)
Lung parenchyma	4.09 (0.50-9.22)
Sinus mucosa	1.78 (1.17-2.49)
Sputum (Multiple dose)	1.28 (0.49-2.38)
Reproductive	
Ejaculate	1.07 (0.86-1.32)
Seminal fluid	1.01 (0.81-1.21)
Vagina	1.22 (0.57-1.63)
Cervix	1.45 (0.56-2.64)

[a]Mean of individual ratios collected over 24 hours following single (100, 150, 200, 300, or 400 mg) or multiple (150 or 200 mg BID) doses of gatifloxacin.

Metabolism

Gatifloxacin undergoes limited biotransformation in humans with less than 1% of the dose excreted in the urine as ethylenediamine and methylethylenediamine metabolites.

In vitro studies with cytochrome P450 isoenzymes (CYP) indicate that gatifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2, suggesting that gatifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes (e.g., midazolam, cyclosporine, warfarin, theophylline).

In vivo studies in animals and humans indicate that gatifloxacin is not an enzyme inducer; therefore, gatifloxacin is unlikely to alter the metabolic elimination of itself or other co-administered drugs.

Excretion

Gatifloxacin is excreted as unchanged drug primarily by the kidney. More than 70% of an administered TEQUIN dose was recovered as unchanged drug in the urine within 48 hours following oral and intravenous administration, and 5% was recovered in

the feces. Less than 1% of the dose is recovered in the urine as two metabolites. Crystals of gatifloxacin have not been observed in the urine of normal, healthy human subjects following administration of intravenous or oral doses up to 800 mg.

The mean elimination half-life of gatifloxacin ranges from 7 to 14 hours and is independent of dose and route of administration. Renal clearance is independent of dose with mean value ranging from 124 to 161 mL/min. The magnitude of this value, coupled with the significant decrease in the elimination of gatifloxacin seen with concomitant probenecid administration, indicates that gatifloxacin undergoes both glomerular filtration and tubular secretion. Gatifloxacin may also undergo minimal biliary and/or intestinal elimination, since 5% of dose was recovered in the feces as unchanged drug. This finding is supported by the 5-fold higher concentration of gatifloxacin in the bile compared to the plasma (mean bile:plasma ratio [range] 5.34 [0.33-14.0]).

Special Populations

Patients with Bacterial Infections

The pharmacokinetics of gatifloxacin were similar between healthy volunteers and patients with infection, when underlying renal function was taken into account (see Table 1).

Geriatric

Following a single oral 400-mg dose of gatifloxacin in young (18-40 years) and elderly (≥65 years) male and female subjects, there were only modest differences in the pharmacokinetics of gatifloxacin noted in female subjects; elderly females had a 21% increase in C_{max} and a 32% increase in $AUC_{(0-\infty)}$ compared to young females. These differences were mainly due to decreasing renal function with increasing age and are not thought to be clinically important. No dosage adjustment based on age alone is necessary for elderly subjects when administering TEQUIN.

Pediatric

The pharmacokinetics of gatifloxacin in pediatric populations (<18 years of age) have not been established.

Gender

Following a single oral 400-mg dose of gatifloxacin in male and female subjects, there were only modest differences in the pharmacokinetics of gatifloxacin, mainly confined to elderly subjects. Elderly females had a 21% increase in C_{max} and a 33% increase in $AUC_{(0-\infty)}$ compared to elderly males. Both results were accounted for by gender-related differences in body weight and are not thought to be clinically important. Dosage adjustment of TEQUIN (gatifloxacin) is not necessary based on gender.

Chronic Hepatic Disease

Following a single oral 400-mg dose of gatifloxacin in healthy subjects and in subjects with moderate hepatic impairment (Child–Pugh B classification of cirrhosis), C_{max} and $AUC_{(0-\infty)}$ values for gatifloxacin were modestly higher (32% and 23% respectively). Due to the concentration-dependent antimicrobial activity associated with quinolones, the modestly higher C_{max} values in the subjects with moderate hepatic impairment are not expected to negatively impact the outcome of TEQUIN therapy in this population. Dosage adjustment of TEQUIN is not necessary in patients with moderate hepatic impairment. The effect of severe hepatic impairment on the pharmacokinetics of TEQUIN (gatifloxacin) is unknown.

Renal Insufficiency

Following administration of a single oral 400-mg dose of gatifloxacin to subjects with varying degrees of renal impairment, apparent total clearance of gatifloxacin (Cl/F) was reduced and systemic exposure (AUC) was increased commensurate with the decrease in renal function (see Table 1). Total gatifloxacin clearance was reduced 57% in moderate renal insufficiency (Cl_{cr} 30-49 mL/min) and 77% in severe renal insufficiency (Cl_{cr} <30 mL/min). Systemic exposure to gatifloxacin was approximately 2 times higher in moderate renal insufficiency and approximately 4 times higher in severe renal insufficiency, compared to subjects with normal renal function. Mean C_{max} values were modestly increased. A reduced dosage of TEQUIN is recommended in patients with creatinine clearance <40 mL/min, including patients requiring hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION: Impaired Renal Function.**)

Diabetes Mellitus

The pharmacokinetics of gatifloxacin in patients with type 2 diabetes (non–insulin-dependent diabetes mellitus), following TEQUIN 400 mg orally for 10 days, were comparable to those in healthy subjects.

Glucose Homeostasis

No clinically significant changes in glucose tolerance (via measurement of oral glucose challenge) and glucose homeostasis (via measurement of fasting serum glucose, serum insulin and c-peptide) were observed following single or multiple intravenous infusion doses of 200 to 800 mg TEQUIN in healthy volunteers, or 400-mg oral doses of TEQUIN for 10 days in patients with type 2 diabetes (non–insulin-dependent diabetes mellitus). Transient modest increases in serum insulin and decreases in glucose concentrations were noted with the first dose of intravenous or oral gatifloxacin. Following multiple oral doses of

TEQUIN in patients with type 2 non–insulin-dependent diabetes mellitus controlled with glyburide, decreases in serum insulin concentrations were noted following oral glucose challenge; however, these decreases were not accompanied by changes in serum glucose levels. (See **PRECAUTIONS: General**.)

Photosensitivity Potential

In a study of the skin response to ultraviolet and visible radiation conducted in 48 healthy, male Caucasian volunteers (12 per group), the minimum erythematous dose was measured for ciprofloxacin (500 mg BID), lomefloxacin (400 mg QD), gatifloxacin (400 mg QD), and placebo before and after drug administration for 7 days. In this study, gatifloxacin was comparable to placebo at all wavelengths tested and had a lower potential for producing delayed photosensitivity skin reactions than ciprofloxacin or lomefloxacin.

Electrocardiogram

In volunteer studies assessing oral and IV doses ranging from 200 to 800 mg, 55 subjects had 76 paired valid ECGs. There were no subjects with abnormal QTc intervals (>450 msec); the mean ± SD change in QTc interval was 2.9 ± 16.5 msec.

There is limited information available on the potential for a pharmacodynamic interaction in humans between gatifloxacin and drugs that prolong the QTc interval of an electrocardiogram. Therefore, gatifloxacin should not be used with Class IA and Class III antiarrhythmics. (See **WARNINGS** and **PRECAUTIONS**.)

Spirometry

No clinically significant changes in spirometry were observed following single or multiple 200-mg, 400-mg, 600-mg, and 800-mg intravenous infusion doses of TEQUIN in healthy volunteers.

Drug-Drug Interactions

Systemic exposure to TEQUIN is increased following concomitant administration of TEQUIN and probenecid, and is reduced by concomitant administration of TEQUIN and ferrous sulfate or antacids containing aluminum or magnesium salts. TEQUIN can be administered 4 hours before the administration of dietary supplements containing zinc, magnesium, or iron (such as multivitamins).

Probenecid: Concomitant administration of TEQUIN (single oral 200-mg dose) with probenecid (500 mg BID x 1 day) resulted in a 42% increase in AUC and a 44% longer half-life of gatifloxacin.

Iron: When TEQUIN (single oral 400-mg dose) was administered concomitantly with ferrous sulfate (single oral 325-mg dose), bioavailability of gatifloxacin was reduced (54% reduction in mean C_{max} and 35% reduction in mean AUC). Administration of TEQUIN (single oral 400-mg dose) 2 hours after or 2 hours before ferrous sulfate (single oral 325-mg dose) did not significantly alter the oral bioavailability of gatifloxacin. (See **DOSAGE AND ADMINISTRATION**.)

Antacids: When TEQUIN (single oral 400-mg dose) was administered 2 hours before, concomitantly, or 2 hours after an aluminum/magnesium-containing antacid (1800 mg of aluminum oxide and 1200 mg of magnesium hydroxide single oral dose), there was a 15%, 69%, and 47% reduction in C_{max} and a 17%, 64%, and 40% reduction in AUC of gatifloxacin, respectively. An aluminum/magnesium-containing antacid did not have a clinically significant effect on the pharmacokinetics of gatifloxacin when administered 4 hours after gatifloxacin administration (single oral 400-mg dose). (See **DOSAGE AND ADMINISTRATION**.)

Milk, Calcium, and Calcium-containing Antacids: No significant pharmacokinetic interactions occur when milk or calcium carbonate is administered concomitantly with TEQUIN. Concomitant administration of 200 mL of milk or 1000 mg of calcium carbonate with TEQUIN (200-mg gatifloxacin dose for the milk study and 400-mg gatifloxacin dose for the calcium carbonate study) had no significant effect on the pharmacokinetics of gatifloxacin. TEQUIN can be administered 4 hours before the administration of dietary supplements containing zinc, magnesium, or iron (such as multivitamins).

Minor pharmacokinetic interactions occur following concomitant administration of gatifloxacin and digoxin; a priori dosage adjustments of either drug are not warranted.

Digoxin: Overall, only modest increases in C_{max} and AUC of digoxin were noted (12% and 19% respectively) in 8 of 11 healthy volunteers who received concomitant administration of TEQUIN (400-mg oral tablet, once daily for 7 days) and digoxin (0.25 mg orally, once daily for 7 days). In 3 of 11 subjects, however, a significant increase in digoxin concentrations was observed. In these 3 subjects, digoxin C_{max} increased by 18%, 29%, and 58% while digoxin AUC increased by 66%, 104%, and 79%, and digoxin clearance decreased by 40%, 51%, and 45%. Although dose adjustments for digoxin are not warranted with initiation of gatifloxacin treatment, patients taking digoxin should be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate. The pharmacokinetics of gatifloxacin was not altered by digoxin.

No significant pharmacokinetic interactions occur when cimetidine, midazolam, theophylline, warfarin, or glyburide is administered concomitantly with TEQUIN. These results and the data from *in vitro* studies suggest that gatifloxacin is unlikely to significantly alter the metabolic clearance of drugs metabolized by CYP3A, CYP1A2, CYP2C9, CYP2C19, and CYP2D6 isoenzymes.

Cimetidine: Administration of TEQUIN (single oral dose of 200 mg) 1 hour after cimetidine (single oral dose of 200 mg) had no significant effect on the pharmacokinetics of gatifloxacin. These results suggest that absorption of gatifloxacin is expected to be unaffected by H_2-receptor antagonists like cimetidine.

Midazolam: TEQUIN administration had no significant effect on the systemic clearance of intravenous midazolam. A single intravenous dose of midazolam (0.0145 mg/kg) had no effect on the steady-state pharmacokinetics of gatifloxacin (once daily oral doses of 400 mg for 5 days). These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP3A4 isoenzyme.

Theophylline: Concomitant administration of TEQUIN (once daily oral doses of 400 mg for 5 days) and theophylline (300 mg BID oral dose for 10 days) had no significant effect on the pharmacokinetics of either drug. These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP1A2 isoenzyme.

Warfarin: Concomitant administration of TEQUIN (once daily oral doses of 400 mg for 11 days) and warfarin (single oral dose of 25 mg) had no significant effect on the pharmacokinetics of either drug nor was the prothrombin time significantly altered. These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP2C9, CYP1A2, CYP3A4, and CYP2C19 isoenzymes. (See **PRECAUTIONS: Drug Interactions**.)

Glyburide: Concomitant administration of TEQUIN (once daily oral doses of 400 mg for 10 days) and glyburide (steady-state once daily regimen) in patients with type 2 diabetes mellitus had no significant effects on the disposition of either drug, nor were the fasting glucose levels significantly changed. These results are consistent with the lack of effect of TEQUIN in *in vitro* studies with the human CYP3A4 isoenzyme.

Microbiology

Gatifloxacin is an 8-methoxyfluoroquinolone with *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The antibacterial action of gatifloxacin results from inhibition of DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme that is involved in the replication, transcription, and repair of bacterial DNA. Topoisomerase IV is an enzyme known to play a key role in the partitioning of the chromosomal DNA during bacterial cell division. It appears that the C-8-methoxy moiety contributes to enhanced activity and lower selection of resistant mutants of gram-positive bacteria compared to the non-methoxy C-8 moiety.

The mechanism of action of fluoroquinolones including gatifloxacin is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines. Therefore, fluoroquinolones may be active against pathogens that are resistant to these antibiotics. There is no cross-resistance between gatifloxacin and the mentioned classes of antibiotics.

From *in vitro* synergy tests, gatifloxacin, as with other fluoroquinolones, is antagonistic with rifampin against enterococci.

Resistance to gatifloxacin *in vitro* develops slowly via multiple-step mutations. Resistance to gatifloxacin *in vitro* occurs at a general frequency of between 1×10^{-7} to 10^{-10}. Although cross-resistance has been observed between gatifloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to gatifloxacin.

Gatifloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin-susceptible strains only)
Streptococcus pneumoniae (penicillin-susceptible strains)

Aerobic gram-negative microorganisms

Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Neisseria gonorrhoeae
Proteus mirabilis

Other microorganisms

Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Gatifloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of ≤2 μg/mL (≤1 μg/mL for *Streptococcus pneumoniae*) against most (90%) strains of the following microorganisms; however, the safety and effectiveness of gatifloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms
- *Staphylococcus saprophyticus*
- *Streptococcus pneumoniae* (penicillin-resistant strains)
- *Streptococcus pyogenes*

Aerobic gram-negative microorganisms
- *Acinetobacter lwoffii*
- *Citrobacter koseri*
- *Citrobacter freundii*
- *Enterobacter aerogenes*
- *Enterobacter cloacae*
- *Klebsiella oxytoca*
- *Morganella morganii*
- *Proteus vulgaris*

Anaerobic microorganisms
- *Peptostreptococcus* species

NOTE: The activity of gatifloxacin against *Treponema pallidum* has not been evaluated; however, other quinolones are not active against *Treponema pallidum* (see **WARNINGS**).

NOTE: Extended-spectrum β-lactamase producing gram-negative microorganisms may have reduced susceptibility to quinolones.

Susceptibility Tests

Dilution techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of gatifloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing *Enterobacteriaceae* and *Staphylococcus* species:

MIC (μg/mL)	Interpretation
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[a]:

MIC (μg/mL)	Interpretation
≤0.5	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[b]:

MIC (μg/mL)	Interpretation
≤1.0	Susceptible (S)
2.0	Intermediate (I)
≥4.0	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Neisseria gonorrhoeae*[c]:

MIC (μg/mL)	Interpretation
≤0.125	Susceptible (S)
0.25	Intermediate (I)
≥0.5	Resistant (R)

[c] These interpretive standards are applicable to agar dilution tests with GC agar base and 1% defined growth supplement.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentration usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard gatifloxacin powder should provide the following MIC values:

Microorganism	MIC Range (μg/mL)
Enterococcus faecalis ATCC 29212	0.12 – 1.0
Escherichia coli ATCC 25922	0.008 – 0.03
Haemophilus influenzae ATCC 49247[d]	0.004 – 0.03
Neisseria gonorrhoeae ATCC 49226[e]	0.002 – 0.016
Pseudomonas aeruginosa ATCC 27853	0.5 – 2.0
Staphylococcus aureus ATCC 29213	0.03 – 0.12
Streptococcus pneumoniae ATCC 49619[f]	0.12 – 0.5

[d] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using HTM.[1]

[e] This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base with 1% defined growth supplement.[1]

[f] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-μg gatifloxacin to test the susceptibility of microorganisms to gatifloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-μg gatifloxacin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing *Enterobacteriaceae* and *Staphylococcus* species:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
15 – 17	Intermediate (I)
≤14	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [g]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)

[g] This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any results other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*[h]:

Zone Diameter (mm)	Interpretation
≥18	Susceptible (S)
15 – 17	Intermediate (I)
≤14	Resistant (R)

[h] These zone diameter standards only apply to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.[2]

For testing *Neisseria gonorrhoeae*[i]:

Zone Diameter (mm)	Interpretation
≥38	Susceptible (S)
34 – 37	Intermediate (I)
≤33	Resistant (R)

[i] These interpretive standards are applicable to disk diffusion tests with GC agar base and 1% defined growth supplement incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for gatifloxacin.[2]

As with standardized dilution techniques, methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-μg gatifloxacin disk should provide the following zone diameters in these laboratory quality control strains:

Microorganism	Zone Diameter Range (mm)
Escherichia coli ATCC 25922	30-37
Haemophilus influenzae ATCC 49247[j]	33-41
Neisseria gonorrhoeae ATCC 49226[k]	45-56
Pseudomonas aeruginosa ATCC 27853	20-28
Staphylococcus aureus ATCC 25923	27-33
Streptococcus pneumoniae ATCC 49619[l]	24-31

[j] This quality control range applies to tests conducted with *Haemophilus influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM)[2].

[k] This quality control range is applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement[2].

[l] This quality control range is applicable only to tests conducted with *S. pneumoniae* ATCC 49619 performed by disk diffusion using Mueller-Hinton agar supplemented with 5% defibrinated sheep blood.

INDICATIONS AND USAGE

TEQUIN (gatifloxacin) is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below. (See **DOSAGE AND ADMINISTRATION.**)

Acute bacterial exacerbation of chronic bronchitis due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis,* or *Staphylococcus aureus.*

Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae.*

Community-acquired pneumonia due to *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae,* or *Legionella pneumophila.*

Uncomplicated urinary tract infections (cystitis) due to *Escherichia coli, Klebsiella pneumoniae, or Proteus mirabilis.*

Complicated urinary tract infections due to *Escherichia coli, Klebsiella pneumoniae,* or *Proteus mirabilis.*

Pyelonephritis due to *Escherichia coli.*

Uncomplicated urethral and cervical gonorrhea due to *Neisseria gonorrhoeae.* **Acute, uncomplicated rectal infections in women** due to *Neisseria gonorrhoeae.* (See **WARNINGS.**)

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to gatifloxacin. Therapy with TEQUIN may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

CONTRAINDICATIONS

TEQUIN is contraindicated in persons with a history of hypersensitivity to gatifloxacin or any member of the quinolone class of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFECTIVENESS OF GATIFLOXACIN IN PEDIATRIC PATIENTS, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.)

GATIFLOXACIN MAY HAVE THE POTENTIAL TO PROLONG THE QTc INTERVAL OF THE ELECTROCARDIOGRAM IN SOME PATIENTS. DUE TO THE LACK OF CLINICAL EXPERIENCE, GATIFLOXACIN SHOULD BE AVOIDED IN PATIENTS WITH KNOWN PROLONGATION OF THE QTc INTERVAL, PATIENTS WITH UNCORRECTED HYPOKALEMIA, AND PATIENTS RECEIVING CLASS IA (E.G., QUINIDINE, PROCAINAMIDE) OR CLASS III (E.G., AMIODARONE, SOTALOL) ANTIARRHYTHMIC AGENTS.

Pharmacokinetic studies between gatifloxacin and drugs that prolong the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants have not been performed. Gatifloxacin should be used with caution when given concurrently with these drugs, as well as in patients with ongoing proarrhythmic conditions, such as clinically significant bradycardia or acute myocardial ischemia. No cardiovascular morbidity or mortality attributable to QTc prolongation occurred with gatifloxacin treatment in over 4000 patients, including 118 patients concurrently receiving drugs known to prolong the QTc interval and 139 patients with uncorrected hypokalemia (ECG monitoring was not performed).

The likelihood of QTc prolongation may increase with increasing concentrations of the drug; therefore, the recommended dose should not be exceeded. QTc prolongation may lead to an increased risk for ventricular arrhythmias including torsades de pointes.

As with other members of the quinolone class, gatifloxacin has caused arthropathy and/or chondrodysplasia in immature dogs. The relevance of these findings to the clinical use of gatifloxacin is unknown. (See **ANIMAL PHARMACOLOGY**.)

Convulsions, increased intracranial pressure, and psychosis have been reported in patients receiving quinolones. Quinolones may also cause central nervous system (CNS) stimulation, which may lead to tremors, restlessness, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, and insomnia. These reactions may occur following the first dose. If these reactions occur in patients receiving gatifloxacin, the drug should be discontinued and appropriate measures instituted. (See **ADVERSE REACTIONS**.)

As with other quinolones, TEQUIN should be used with caution in patients with known or suspected CNS disorders, such as severe cerebral atherosclerosis, epilepsy, and other factors that predispose to seizures.

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones. These reactions may occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.

TEQUIN should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated. (See **PRECAUTIONS**.)

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have been reported in patients receiving antibacterial therapy. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome); vasculitis, arthralgia, myalgia, serum sickness; allergic pneumonitis, interstitial nephritis; acute renal insufficiency or failure; hepatitis, jaundice, acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including TEQUIN, and may range in severity from mild to life-threatening. It is important, therefore, to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is the primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Although not seen in clinical trials of TEQUIN, ruptures of the shoulder, hand, and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones. TEQUIN should be discontin-

ued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones.

Gatifloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis.

PRECAUTIONS

General

Quinolones may cause central nervous system (CNS) events including nervousness, agitation, insomnia, anxiety, nightmares, or paranoia. (See **WARNINGS** and **PRECAUTIONS: Information for Patients**.)

Administer gatifloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of gatifloxacin may be reduced. In patients with impaired renal function (creatinine clearance <40 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of gatifloxacin due to decreased clearance. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic (e.g., glyburide) or with insulin. In these patients, the monitoring of blood glucose is recommended. (See **CLINICAL PHARMACOLOGY** and **ADVERSE REACTIONS**.)

Information for Patients (See **Patient Information** Section)

To assure safe and effective use of TEQUIN, the following information and instructions should be communicated to the patient when appropriate.

Patients should be advised:

- that TEQUIN may produce changes in the electrocardiogram (QTc interval prolongation);
- that TEQUIN should be avoided in patients receiving Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic agents;
- that TEQUIN should be used with caution in patients receiving drugs that may effect the QTc interval such as cisapride, erythromycin, antipsychotics, and tricyclic antidepressants;
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, or recent myocardial ischemia;
- to inform their physician of any other medications when taken concurrently with TEQUIN, including over-the-counter medications;
- to contact their physician if they experience palpitations or fainting spells while taking TEQUIN;
- that TEQUIN Tablets may be taken with or without meals;
- that TEQUIN Tablets should be taken 4 hours before any aluminum- or magnesium-based antacids (see **PRECAUTIONS: Drug Interactions**);
- that TEQUIN Tablets should be taken at least 4 hours before the administration of ferrous sulfate or dietary supplements containing zinc, magnesium, or iron (such as multivitamins) (see **PRECAUTIONS: Drug Interactions**);
- that TEQUIN should be taken 4 hours before VIDEX® (didanosine) buffered tablets, buffered solution, or buffered powder for oral suspension;
- that TEQUIN may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction (see **WARNINGS** and **ADVERSE REACTIONS**);
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue gatifloxacin and consult a physician (see **PRECAUTIONS: General**).
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon;
- that TEQUIN may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination;
- that phototoxicity has been reported in patients receiving certain quinolones. There was no phototoxicity seen with TEQUIN at the recommended dose. In keeping with good medical practice, avoid excessive sunlight or artificial ultraviolet light (e.g., tanning beds). If sunburn-like reaction or skin eruptions occur, contact their physician. (See **CLINICAL PHARMACOLOGY: Photosensitivity Potential**.)

- that convulsions have been reported in patients receiving quinolones, and they should notify their physician before taking this drug if there is a history of this condition.

Drug Interactions

TEQUIN (gatifloxacin) can be taken 4 hours before ferrous sulfate, dietary supplements containing zinc, magnesium, or iron (such as multivitamins), or aluminum/magnesium-containing antacids without any significant pharmacokinetic interactions. (See **CLINICAL PHARMACOLOGY**.)

Milk, calcium carbonate, cimetidine, theophylline, warfarin, glyburide, or midazolam: No significant interactions have been observed when administered concomitantly with TEQUIN. No dosage adjustments are necessary when these drugs are administered concomitantly with TEQUIN. (See **CLINICAL PHARMACOLOGY**.)

Digoxin: Concomitant administration of TEQUIN and digoxin did not produce significant alteration of the pharmacokinetics of gatifloxacin; however, an increase in digoxin concentrations was observed for 3 of 11 subjects. Patients taking digoxin should therefore be monitored for signs and/or symptoms of toxicity. In patients who display signs and/or symptoms of digoxin intoxication, serum digoxin concentrations should be determined, and digoxin dosage should be adjusted as appropriate. (See **CLINICAL PHARMACOLOGY**.)

Probenecid: The systemic exposure of TEQUIN is significantly increased following the concomitant administration of TEQUIN and probenecid. (See **CLINICAL PHARMACOLOGY**.)

Warfarin: In subjects receiving warfarin, no significant change in clotting time was observed when gatifloxacin was coadministered. However, because some quinolones have been reported to enhance the effects of warfarin or its derivatives, prothrombin time or other suitable anticoagulation test should be monitored closely if a quinolone antimicrobial is administered with warfarin or its derivatives.

Nonsteroidal anti-inflammatory drugs (NSAIDS): Although not observed with gatifloxacin in preclinical and clinical trials, the concomitant administration of nonsteroidal anti-inflammatory drugs with a quinolone may increase the risks of CNS stimulation and convulsions (see **WARNINGS**).

Laboratory Test Interactions

There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

B6C3F1 mice given gatifloxacin in the diet for 18 months at doses with an average intake of up to 81 mg/kg/day in males and 90 mg/kg/day in females showed no increases in neoplasms. These doses are approximately 0.13 and 0.18 times the maximum recommended human dose based upon daily systemic exposure (AUC).

In a 2-year dietary carcinogenicity study in Fischer 344 rats, no increases in neoplasms were seen in males given doses up to 47 mg/kg/day and females given up to 139 mg/kg/day. These doses are approximately 0.36 (males) and 0.81 (females) times the maximum recommended human dose based upon daily systemic exposure. A statistically significant increase in the incidence of large granular lymphocyte (LGL) leukemia was seen in males treated with a high dose of 100 mg/kg/day (approximately 0.74 times the maximum recommended human dose based upon daily systemic exposure) versus controls. Although Fischer 344 rats have a high spontaneous background rate of LGL leukemia, the incidence in high-dose males slightly exceeded the historical control range established for this strain. The findings in high-dose males are not considered a concern with regard to the safe use of gatifloxacin in humans.

In genetic toxicity tests, gatifloxacin was not mutagenic in several strains of bacteria used in the Ames test; however, it was mutagenic to *Salmonella* strain TA102. Gatifloxacin was negative in four *in vivo* assays that included oral and intravenous micronucleus tests in mice, an oral cytogenetics test in rats, and an oral DNA repair test in rats. Gatifloxacin was positive in *in vitro* gene-mutation assays in Chinese hamster V-79 cells and *in vitro* cytogenetics assays in Chinese hamster CHL/IU cells. These findings were not unexpected; similar findings have been seen with other quinolones and may be due to the inhibitory effects of high concentrations on eukaryotic type II DNA topoisomerase.

There were no adverse effects on fertility or reproduction in rats given gatifloxacin orally at doses up to 200 mg/kg/day (approximately equivalent to the maximum human dose based on systemic exposure [AUC]).

Pregnancy: Category C

There were no teratogenic effects observed in rats or rabbits at oral gatifloxacin doses up to 150 or 50 mg/kg, respectively (approximately 0.7 and 1.9 times the maximum human dose based on systemic exposure). However, skeletal malformations were observed in fetuses from rats given 200 mg/kg/day orally or 60 mg/kg/day intravenously during organogenesis. Developmental delays in skeletal ossification, including wavy ribs, were observed in fetuses from rats given oral doses of ≥150 mg/kg or intravenous doses of ≥30 mg/kg daily during organogenesis, suggesting that gatifloxacin is slightly fetotoxic at these doses. Similar findings have been seen with other quinolones. These changes were not seen in rats or rabbits

given oral doses of gatifloxacin up to 50 mg/kg (approximately 0.2 and 1.9 times the maximum human dose, respectively, based on systemic exposure).

When rats were given oral doses of 200 mg/kg of gatifloxacin beginning in late pregnancy and continuing throughout lactation, late postimplantation loss increased, as did neonatal and perinatal mortalities. These observations also suggest fetotoxicity. Similar findings have been seen with other quinolones.

Because there are no adequate and well-controlled studies in pregnant women, TEQUIN should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers

Gatifloxacin is excreted in the breast milk of rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when gatifloxacin is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of gatifloxacin in pediatric populations (<18 years of age) have not been established. Quinolones, including gatifloxacin, cause arthropathy and osteochondrotoxicity in juvenile animals (rats and dogs).

Geriatric Use

In multiple-dose clinical trials of gatifloxacin (N=2891), 22% of patients were ≥65 years of age and 10% were ≥75 years of age. No overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **DOSAGE AND ADMINISTRATION**.)

ADVERSE REACTIONS

Over 4000 patients have been treated with gatifloxacin in single- and multiple-dose clinical efficacy trials worldwide.

In gatifloxacin studies, the majority of adverse reactions were described as mild in nature. Gatifloxacin was discontinued for adverse events thought related to drug in 2.9% of patients.

Drug-related adverse events classified as possibly, probably, or definitely related with a frequency of ≥3% in patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows: nausea 8%, vaginitis 6%, diarrhea 4%, headache 3%, dizziness 3%.

In patients who were treated with either intravenous gatifloxacin or with intravenous followed by oral therapy, the incidence of adverse events was similar to those who received oral therapy alone. Local injection site reactions (redness at injection site) were noted in 5% of patients.

Additional drug-related adverse events (possibly, probably, or definitely related) considered clinically relevant that occurred in ≥0.1% to <3% of patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows:

Body as a Whole: allergic reaction, chills, fever, back pain, chest pain
Cardiovascular System: palpitation
Digestive System: abdominal pain, constipation, dyspepsia, glossitis, oral moniliasis, stomatitis, mouth ulcer, vomiting
Metabolic/Nutritional System: peripheral edema
Nervous System: abnormal dream, insomnia, paresthesia, tremor, vasodilatation, vertigo
Respiratory System: dyspnea, pharyngitis
Skin/Appendages: rash, sweating
Special Senses: abnormal vision, taste perversion, tinnitus
Urogenital System: dysuria, hematuria

Additional drug-related adverse events considered clinically relevant that occurred in <0.1% (rare adverse events) of patients receiving gatifloxacin in single- and multiple-dose clinical trials are as follows: abnormal thinking, agitation, alcohol intolerance, anorexia, anxiety, arthalgia, arthritis, asthenia, asthma (bronchospasm), ataxia, bone pain, bradycardia, breast pain, cheilitis, colitis, confusion, convulsion, cyanosis, depersonalization, depression, diabetes mellitus, dry skin, dysphagia, ear pain, ecchymosis, edema, epistaxis, euphoria, eye pain, face edema, flatulence, gastritis, gastrointestional hemorrhage, gingivitis, halitosis, hallucination, hematemesis, hostility, hyperesthesia, hyperglycemia, hypertension, hypertonia, hyperventilation, hypoglycemia, leg cramp, lymphadenopathy, maculopapular rash, metrorrhagia, migraine, mouth edema, myalgia, myasthenia, neck pain, nervousness, panic attack, paranoia, parosmia, pruritus, pseudomembranous colitis, psychosis, ptosis, rectal hemorrhage, somnolence, stress, substernal chest pain, tachycardia, taste loss, thirst, tongue edema, vesiculobullous rash.

Laboratory Changes

Clinically relevant changes in laboratory parameters, without regard to drug relationship, occurred in fewer than 1% of TEQUIN-treated patients. These included the following: neutropenia, increased ALT or AST levels, alkaline phosphatase, bilirubin, serum amylase, and electrolytes abnormalities. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

OVERDOSAGE

Gatifloxacin exhibits a low potential for acute toxicity in animal studies. The minimum lethal oral doses in rats and dogs were greater than 2000 mg/kg and 1000 mg/kg, respectively. The minimum lethal intravenous dose was 144 mg/kg in rats and greater than 45 mg/kg in dogs. Clinical signs observed included decreased activity and respiratory rate, vomiting, tremors, and convulsions.

In the event of acute oral overdose, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed (including ECG monitoring) and given symptomatic and supportive treatment. Adequate hydration should be maintained. Gatifloxacin is not efficiently removed from the body by hemodialysis (approximately 14% recovered over 4 hours) or by chronic ambulatory peritoneal dialysis (CAPD) (approximately 11% recovered over 8 days).

DOSAGE AND ADMINISTRATION

The recommended dosage for TEQUIN Tablets or TEQUIN Injection is described in Table 4. Doses of TEQUIN are administered once every 24 hours. These recommendations apply to all patients with a creatinine clearance ≥40 mL/min. For patients with a creatinine clearance <40 mL/min, see the **Impaired Renal Function** subsection.

TEQUIN can be administered without regard to food, including milk and dietary supplements containing calcium.

Oral doses of TEQUIN should be administered at least 4 hours before the administration of ferrous sulfate, dietary supplements containing zinc, magnesium, or iron (such as multivitamins), aluminum/magnesium-containing antacids, or VIDEX® (didanosine) buffered tablets, buffered solution, or buffered powder for oral suspension.

TEQUIN can be administered without regard to age (≥18 years) or gender.

When switching from intravenous to oral dosage administration, no dosage adjustment is necessary. Patients whose therapy is started with TEQUIN Injection may be switched to TEQUIN Tablets when clinically indicated at the discretion of the physician.

TEQUIN Injection should be administered by INTRAVENOUS infusion only. It is not intended for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Single-use vials require dilution prior to administration. (See *Preparation of Gatifloxacin for Intravenous Administration.*)

TEQUIN Injection should be administered by intravenous infusion over a period of 60 minutes. CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION SHOULD BE AVOIDED.

Table 4
Gatifloxacin – Dosage Guidelines

Infection[a]	Daily Dose[b]	Duration
Acute Bacterial Exacerbation of Chronic Bronchitis	400 mg	7-10 days
Acute Sinusitis	400 mg	10 days
Community-acquired Pneumonia	400 mg	7-14 days
Uncomplicated Urinary Tract Infections (cystitis)	400 mg or 200 mg	Single dose 3 days
Complicated Urinary Tract Infections	400 mg	7-10 days
Acute Pyelonephritis	400 mg	7-10 days
Uncomplicated Urethral Gonorrhea in Men; Endocervical and Rectal Gonorrhea in Women	400 mg	Single dose

[a] due to the designated pathogens (see **INDICATIONS AND USAGE**).
[b] for either the oral or intravenous routes of administration for TEQUIN (see **CLINICAL PHARMACOLOGY**).

Impaired Renal Function

Since gatifloxacin is eliminated primarily by renal excretion, a dosage modification of TEQUIN is recommended for patients with creatinine clearance <40 mL/min, including patients on hemodialysis and on CAPD. The recommended dosage of TEQUIN (gatifloxacin) is:

Table 5
Recommended Dosage of TEQUIN in Adult Patients with Renal Impairment

Creatinine Clearance	Initial Dose	Subsequent Dose[a]
≥40 mL/min	400 mg	400 mg every day
<40 mL/min	400 mg	200 mg every day
Hemodialysis	400 mg	200 mg every day
Continuous peritoneal dialysis	400 mg	200 mg every day

[a] Start subsequent dose on Day 2 of dosing.

Administer TEQUIN after a dialysis session for patients on hemodialysis.

Single 400-mg dose TEQUIN regimen (for the treatment of uncomplicated urinary tract infections and gonorrhea) and 200 mg once daily for 3 days TEQUIN regimen (for the treatment of uncomplicated urinary tract infections) require no dosage adjustment in patients with impaired renal function.

The following formula may be used to estimate creatinine clearance:

$$\text{Men: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Women: 0.85 x the value calculated for men.

Chronic Hepatic Disease

No adjustment in the dosage of TEQUIN is necessary in patients with moderate hepatic impairment (Child-Pugh Class B). There are no data in patients with severe hepatic impairment (Child-Pugh Class C). (See **CLINICAL PHARMACOLOGY**.)

Intravenous Administration

Preparation of Gatifloxacin for Intravenous Administration

TEQUIN solution in single-use vials: TEQUIN Injection is supplied in single-use 20 or 40 mL vials (10 mg/mL) containing a concentrated solution of gatifloxacin in 5% dextrose (200 or 400 mg of gatifloxacin, respectively). (See **HOW SUPPLIED**.) THESE TEQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION. The concentration of the resulting diluted solution should be 2 mg/mL prior to administration.

Compatible intravenous solutions: Any of the following intravenous solutions may be used to prepare a 2 mg/mL gatifloxacin solution:

5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
Lactated Ringer's and 5% Dextrose Injection, USP
5% Sodium Bicarbonate Injection, USP
Plasma Lyte 56/5% Dextrose Injection®, USP
M/6 Sodium Lactate Injection, USP
Water for Injection, USP

Gatifloxacin solutions at 2 mg/mL also have been shown to be compatible with 20 mEq/L Potassium Chloride in 5% Dextrose and 0.45% Sodium Chloride Injection, USP.

This intravenous drug product should be inspected visually for particulate matter prior to dilution and administration. Samples containing visible particles should be discarded. Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. Since the vials are for single-use only, any unused portion remaining in the vial should be discarded.

Since only limited data are available on the compatibility of gatifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to TEQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.

If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of TEQUIN Injection with an infusion solution compatible with TEQUIN Injection and with any other drug(s) administered via this common line.

If TEQUIN Injection is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

TEQUIN Injection premix in single-use flexible containers: TEQUIN Injection is also available in ready-to-use 100- and 200-mL flexible bags containing a dilute solution of 200 or 400 mg gatifloxacin in 5% dextrose. NO FURTHER DILUTION OF THIS PREPARATION IS NECESSARY.

This intravenous drug product should be inspected visually for particulate matter prior to dilution and administration. Samples containing visible particles should be discarded.

Since the premix flexible bags are for single use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of gatifloxacin intravenous injection with other intravenous substances, additives or other medications should not be added to TEQUIN Injection in flexible containers or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of TEQUIN Injection with an infusion solution compatible with TEQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the use of TEQUIN Injection premix in flexible containers:

To open:

1. Tear outer wrap at the notch and remove solution container.
2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.
3. Use only if solution is clear and light yellow to greenish-yellow in color.
4. Use sterile equipment.
5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.
   NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of TEQUIN Injection premix in flexible containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

Stability of TEQUIN Injection as Supplied

When stored under recommended conditions, TEQUIN Injection, as supplied in 20-mL and 40-mL vials and in 100-mL and 200-mL flexible containers, is stable through the expiration date printed on the label.

Stability of TEQUIN Injection Following Dilution

TEQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 2 mg/mL, is stable for 14 days when stored between 20° C - 25° C or when stored under refrigeration between 2° C - 8° C.

TEQUIN Injection, when diluted to a concentration of 2 mg/mL in a compatible intravenous fluid EXCEPT FOR 5% SODIUM BICARBONATE INJECTION, USP, may be stored for up to six months at -25° C - 10° C (-13° F - 14° F). Frozen solutions may be thawed at controlled room temperature. Solutions that have been thawed are stable for 14 days after removal from the freezer when stored between 20° C - 25° C or when stored under refrigeration between 2° C - 8° C. Solutions should not be refrozen.

HOW SUPPLIED

Tablets

TEQUIN™ Tablets are available as 200-mg and 400-mg white, film-coated tablets. The tablets are almond shaped and biconvex and contain gatifloxacin sesquihydrate equivalent to either 200 mg or 400 mg gatifloxacin.

TEQUIN Tablets (gatifloxacin) are packaged in bottles and unit dose blister strips in the following configurations:

200 mg tablets—color: white; shape: biconvex; debossing: "BMS" on one side and "TEQUIN" and "200" on the other.
Bottles of 30 (NDC 0015-1117-50)
Blister pack of 100 (NDC 0015-1117-80)

400 mg tablets—color: white; shape: biconvex; debossing: "BMS" on one side and "TEQUIN" and "400" on the other.
Bottles of 50 (NDC 0015-1177-60)
Blister pack of 100 (NDC 0015-1177-80)

Storage
Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature].

Intravenous Solution—Single-use Vials
TEQUIN™ Injection (gatifloxacin) is available for intravenous administration in the following configurations:
Single-use vials containing a clear, light yellow to greenish-yellow solution at a concentration of 10 mg/mL gatifloxacin.
10 mg/mL (200 mg), 20-mL vials (NDC 0015-1178-80)
10 mg/mL (400 mg), 40-mL vials (NDC 0015-1179-80)

Storage
Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature].

Intravenous Solution—Premix Bags
TEQUIN Injection is also available in ready-to-use flexible bags containing a dilute solution of 200 mg or 400 mg of gatifloxacin in 5% dextrose. Premix bags are manufactured by Abbott Laboratories in North Chicago, IL.
2 mg/mL (200 mg), 100-mL flexible container (NDC 0015-1180-80)
2 mg/mL (400 mg), 200-mL flexible container (NDC 0015-1181-80)

Storage
Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature]. Do not freeze.

ANIMAL PHARMACOLOGY
In contrast to some other quinolone antibacterials, there was no evidence of phototoxicity when gatifloxacin was evaluated in the hairless mouse or guinea pig models using simulated sunlight or UVA radiation, respectively.

Unlike some other members of the quinolone class, crystalluria, ocular toxicity, and testicular degeneration were not observed in 6-month repeat dose studies with rats or dogs given gatifloxacin.

While some quinolone antibacterials have proconvulsant activity that is exacerbated with concomitant use of nonsteroidal antiinflammatory drugs (NSAID), gatifloxacin did not produce an increase in seizure activity when administered intravenously to mice at doses up to 100 mg/kg in combination with the NSAID fenbufen.

Quinolone antibacterials have been shown to cause arthropathy in immature animals. There is no evidence of arthropathy in fully mature rats and dogs given gatifloxacin for 6 months at doses of 240 or 24 mg/kg, respectively (approximately 1.5 times the maximum human dose in both species based on systemic exposure). Arthropathy and chondrodysplasia were observed in immature dogs given 10 mg/kg gatifloxacin orally for 7 days (approximately equal to the maximum human dose based upon systemic exposure) [see **WARNINGS**]. The relevance of these findings to the clinical use of gatifloxacin is unknown.

Some members of the quinolone class have been shown to cause prolongation of the QT interval in dogs. Intravenous 10-mg/kg bolus doses of gatifloxacin had no effect on QT interval, in anesthetized dogs.

REFERENCES
1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grows Aerobically* - Fourth Edition; Approved Standard, NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Sixth Edition; Approved Standard, NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January 1997.

Patient Information About:

TEQUIN™

(gatifloxacin)

200 mg and 400 mg Tablets

This section contains important information about TEQUIN (gatifloxacin) that you should read before you begin treatment. This section does not list all the benefits and risks of TEQUIN and does not take the place of discussions with your doctor or healthcare professional about your medical condition or your treatment. If you have questions, talk with your healthcare professional. The medicine described here can only be prescribed by a licensed healthcare professional. Only your healthcare professional can determine if TEQUIN is right for you.

What is TEQUIN?

TEQUIN (pronounced TEK win) is an antibiotic used to treat lung, sinus, or urinary tract infections, and also to treat certain sexually transmitted diseases caused by germs called bacteria. TEQUIN kills many of the kinds of bacteria that can infect the lungs, sinus, and urinary tract and that cause certain sexually transmitted diseases. TEQUIN has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses, rather than bacteria, may infect the lungs and sinuses (for example, the common cold). TEQUIN, like all other antibiotics, does not kill viruses.

The sexually transmitted disease called gonorrhea is treated by TEQUIN. Other diseases called syphilis or non-gonococcal disease are not treated by TEQUIN.

You should contact your doctor if you think your condition is not improving while taking TEQUIN. TEQUIN Tablets are white and contain either 200 mg or 400 mg of active drug.

How and When Should I Take TEQUIN?

TEQUIN should be taken once a day for 1 to 14 days depending on your prescription. It should be swallowed whole and may be taken with or without food. Try to take the tablet at the same time each day.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of TEQUIN. Try not to miss a dose, but if you do, take it as soon as possible. If it is almost time for the next dose, skip the missed dose and continue your regular dose.

Who should not take TEQUIN?

You should avoid TEQUIN if you have ever had a severe allergic reaction to any medicine in the group of antibiotics known as "quinolones" such as CIPRO® (ciprofloxacin) or LEVAQUIN® (levofloxacin).

You should avoid TEQUIN if you have a rare condition known as congenital prolongation of the QTc interval. If any of your family members have this condition, you should inform your healthcare professional.

You should avoid TEQUIN if you are being treated for heart rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone, or sotalol. Inform your healthcare professional if you are taking a heart rhythm drug.

TEQUIN should be avoided in patients with a condition known as hypokalemia (low blood potassium). Hypokalemia may be caused by medicines called diuretics such as furosemide and hydrochlorothiazide. If you are taking a diuretic you should speak with your healthcare professional.

If you are pregnant or planning to become pregnant while taking TEQUIN, talk to your doctor before taking this medication. TEQUIN is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

TEQUIN is not recommended for children.

What about other medications I am taking?

It is important to let your healthcare provider know all of the medicines that you are using.

- It is important to let your healthcare provider know if you are taking certain medicines that can have an effect on an electrocardiogram test, such as cisapride, erythromycin, some antidepressants, and some antipsychotic drugs.
- You should tell your healthcare professional if you are taking medicines called diuretics (also sometimes called water pills) such as furosemide and hydrochlorothiazide, because diuretics can sometimes cause low potassium.
- Many antacids and multivitamins may interfere with the absorption of TEQUIN and may prevent it from working properly. You should take TEQUIN 4 hours before taking these products.

What are the possible side effects of TEQUIN?

TEQUIN is generally well tolerated. The most common side effects that can occur when taking TEQUIN are usually mild, and include nausea, vomiting, stomach pain, diarrhea, dizziness, and headache. You should be careful about driving or operating machinery until you are sure TEQUIN does not cause dizziness. If you notice any side effects not mentioned in this section or if you have any question or concerns about the side effects you are experiencing, please discuss them with your healthcare professional.

In a few people, TEQUIN, like some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this has not caused any problems in more than 4000 patients who have taken TEQUIN in clinical trials, in theory, it could result in extremely rare cases of abnormal heartbeat, that may be dangerous. Contact your healthcare professional if you develop heart palpitations (fast beating), or have fainting spells.

Where Can I Get More Information about TEQUIN?

This section is a summary of the most important information about TEQUIN. It does not include everything there is to know about TEQUIN. If you have any questions or problems, you should talk to your doctor or healthcare provider. There is also a leaflet (Package Insert) written for healthcare professionals that your pharmacist can let you read. You may want to read this information and discuss it with your doctor or other healthcare professional. Remember, no written information can replace careful discussion with your doctor.

Remember

- Take your dose of TEQUIN once a day.
- Complete the course of medication (take all of the pills) even if you are feeling better.
- Do not use TEQUIN for another condition or give it to others.
- Store TEQUIN tablets at room temperature in a tightly sealed container.
- Throw away TEQUIN when it is outdated or no longer needed by flushing it down the toilet.
- Keep this and all medications out of reach of children.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

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117880DIM-02 51-008627-01
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Issued: December 1999

United States Patent [19]

Masuzawa et al.

[11] **Patent Number: 4,980,470**

[45] **Date of Patent: Dec. 25, 1990**

[54] **8-ALKOXYQUINOLONECARBOXYLIC ACID AND SALTS THEREOF**

[75] Inventors: **Kuniyoshi Masuzawa**, Koga; **Seigo Suzue**; **Keiji Hirai**, both of Kuki; **Takayoshi Ishizaki**, Saitama, all of Japan

[73] Assignee: **Kyorin Pharmaceutical Co., Ltd.**, Tokyo, Japan

[21] Appl. No.: **3,822**

[22] Filed: **Jan. 16, 1987**

[30] **Foreign Application Priority Data**

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Sep. 18, 1986 [JP] Japan 1-220149

[51] **Int. Cl.**[5] **C07D 403/04; C07D 401/04**
[52] **U.S. Cl.** **544/363**; 544/225; 544/226; 546/8; 546/156
[58] **Field of Search** 544/363; 546/156

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,665,079 5/1987 Culbertson et al. 546/156
4,822,801 4/1989 Domagala et al. 546/156

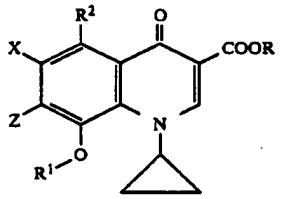
FOREIGN PATENT DOCUMENTS

0106489 4/1984 European Pat. Off. .
0126355 11/1984 European Pat. Off. .
0132845 2/1985 European Pat. Off. .
0153163 8/1985 European Pat. Off. .
0153828 9/1985 European Pat. Off. .

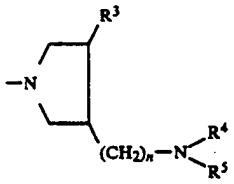
Primary Examiner—Richard L. Raymond
Assistant Examiner—James H. Turnipseed
Attorney, Agent, or Firm—Oblon, Fisher, Spivak, McClelland & Maier

[57] **ABSTRACT**

Quinolonecarboxylic acid derivatives of the following formula:



wherein R indicates a hydrogen atom or lower alkyl group, R^1 indicates a lower alkyl group, R^2 indicates a hydrogen atom, amino group or nitro group, X indicates a halogen atom, and Z indicates a halogen atom, piperazino group, N-methylpiperazino group, 3-methylpiperazino group, 3-hydroxypyrrolidino group, or pyrrolidino group of the following formula,



(here, n is 0 or 1, R^3 indicates a hydrogen atom or lower alkyl group, R^4 indicates a hydrogen atom, lower alkyl group and R^5 indicates a hydrogen atom, lower alkyl group, acyl group or alkoxycarbonyl group), the hydrates and pharmaceutically acceptable salts thereof are useful as antibacterial agents.

8 Claims, No Drawings

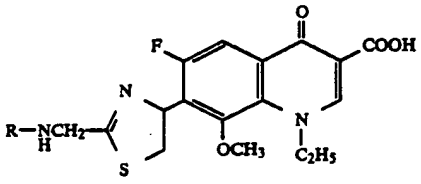
8-ALKOXYQUINOLONECARBOXYLIC ACID AND SALTS THEREOF

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel quinolonecarboxylic acid derivatives having excellent properties as antibacterial agent, process for their preparation, and antibacterial agents containing these novel compounds.

Compounds of this invention are characterized in having a cyclopropyl group on 1-position and an alkoxy group on 8-position of the quinolonecarboxylic acid.

With respect to the 8-alkoxyquinolonecarboxylic acid derivatives, following 8-methoxy derivatives were described previously in Japanese Unexamined Patent Publication No. Sho 60-214773.



(R = H, CH_3)

However, the antibacterial activity of those compounds is weak and their other favoable properties for antibacterial agents have not been described.

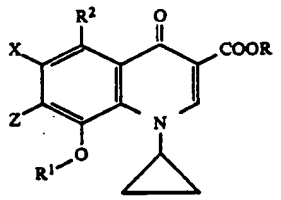
Recently, norfloxacin, which has been developed by us, shows high antibacterial activity against gram-negative bacteria including *Pseudomonas aeruginosa* and gram-positive bacteria. This compound is widely used clinically as new quinolonecarboxylic acid-antibacterial agent having a broad antibacterial spectrum. Afterwards, efforts are focusing on improvement of bioavailability of norfloxacin or strengthing its antibacterial activity.

Consequently, quinolonecarboxylic acid derivatives, having similar substituents, such as ofloxacin and ciprofloxacin have been developed. These new quinolonecarboxylic acid derivatives show more excellent antibacterial activity against gram-negative bacteria than other antibacterial agents such as β-lactam and aminoglycoside antibiotics. Moreover, the development and spread of resistance to new quinolonecartoxylic acids is not easy as compared with that of other antibacterial agents. However, their activity against gram-positive bacteria are weak compared with those against gram-negative bacteria. Therefore, these quinolonecarboxylic acids have unfortunately solved the clinical problem of increase in the isolation frequency of gram-positive bacteria from clinical materials. From the results of various studies, the inventors found that some of the quinolonecarboxylic acid derivatives having excellent antibacterial activity can not use as medicinal drug because of their toxicity, and that excellent selective toxicity is important factor as well as antibacterial activity.

As the results of diligent studies focusing on the dissolution these problem and on the development of useful new medicinal drugs, the inventors have found novel compounds of this invention exhibit extremely high activity against aerobic gram-negative and -positive bacteria, and besides anaerobic bacteria and Mycoplasma that show less susceptibility to conventional quinolonecarboxylic acids. Furthermore, these compounds show not only high selective toxicity between prokaryotic cells and eukaryotic cells, but also the excellent absorption when administered to animals orally. The compounds of this invention do not exhibit any toxicological effects after oral or parenteral administration.

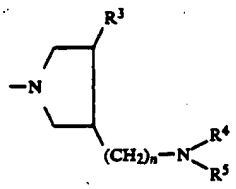
These indicates that the compounds of this invention are very useful as the medicinal drugs for human being and domestic animals, and further as antibacterial agents for fish and shellfish, and plants.

The invention provides 8-alkoxyquinolonecarboxylic acid derivatives represented by a general formula (I),



(I)

wherein R indicates a hydrogen atom or lower alkyl group, R^1 indicates a lower alkyl group, R^2 indicates a hydrogen atom, amino group or nitro group, X indicates a halogen atom, and Z indicates a halogen atom, piperazino group, N-methylpiperazino group, 3-methylpiperazino group, 3-hydroxypyrrolidino group, or pyrrolidino group of the following formula,



(here, n is 0 or 1, R^3 indicates a hydrogen atom or lower alkyl group, R^4 indicates a hydrogen atom, lower alkyl group or substituted lower alkyl group and R^5 indicatesa hydrogen atom, lower alkyl group, acyl group or alkoxycarbonyl group), the hydrates or the pharmaceutically acceptable acid addition or alkali salts thereof.

Here, the lower alkyl group means a straight or branched alkyl group having carbon atom of 1 to 5, for example, methyl group, ethyl group, isopropyl group, n-butyl group, t-butyl group, amyl group, isoamyl group or the like.

Moreover, the halogen atom means a fluorine atom, chlorine atom, bromine atom or iodine atom, preferably fluorine atom, chlorine atom or bromine atom.

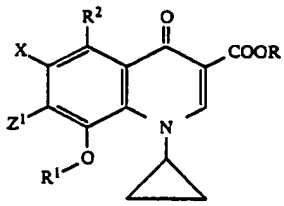
The acyl group means an aliphatic or aromatic acyl group having carbon atoms of 1 to 10, for example, formyl group, acetyl group, benzoyl group or the like.

The alkoxycarbonyl group means an aliphatic or aromatic alkoxycarbonyl group having carbon atoms of 1 to 10, for example, ethoxycarbonyl group, t-butoxycarbonyl group, benzyloxycarbonyl group or the like.

The substituted lower alkyl group means a previously defined alkyl group being substituted with hydroxy group or halogen atom, for example, hydroxyethyl group, fluoroethyl group or the like.

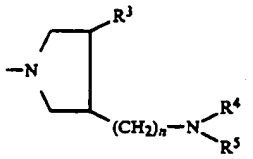
In following, the processes of preparing the compounds of the invention will be explained.

Compounds represented by a general formula (IV);

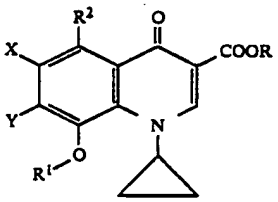


(IV)

wherein R, R^1, R^2 and X are same as above, and Z^1 indicates a piperazino group, N-methylpiperazino group, 3-methylpiperazino group, 3-hydroxypyrrolidino group, or pyrrolidino group of the following formula,



(here, n, R^3, R^4 and R^5 are same as above.) are prepared by allowing compounds represented by a general formula (II);



(II)

wherein Y indicates a halogen atom, and R, R^1, R^2 and X are same as above, to condense with cyclic amines represented by a general formula (III);

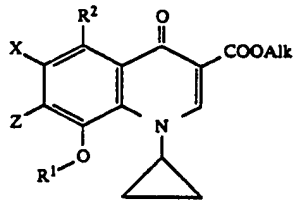
$$Z^1\text{—H} \qquad \text{(III)}$$

wherein Z^1 is same as above.

The reaction between the compounds represented by the formula (II) and the compounds represented by the formula (III) can be conducted in the absence of solvent or in the presence of polar solvents such as water, alcohols, acetonitrile, dimethylformamdide (DMF), dimethyl sulfoxide (DMSO), hexamethylphosphoric amide (HMPA), pyridine, picoline, etc. The reaction temperature is selected appropriately within a range of room temperature to 200° C., preferably room temperature to 160° C. In more detail, it is suitable to allow the compounds represented by the formula (II) to react with 1 to 5 times mole of the compounds represented by the formula (III) for 1 to 50 hours at room temperature to 120° C. in 2 to 10 times volume of the solvents aforementioned per volume of the compound (II).

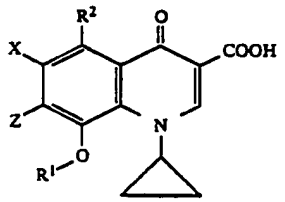
At this time, the use of deacidifying agents such as triethylamine, diazabicyclo bases and potassium carbonate is also preferable.

Moreover, in the case of compounds in which R is a lower alkyl group, that is, compounds represented by a general formula (V);



(V)

wherein Alk indicates a lower alkyl group, and R^1, R^2, X and Z are same as above, among the compounds represented by the general formula (I), they are converted to quinolonecarboxylic acid derivatives represented by a general formula (VI);

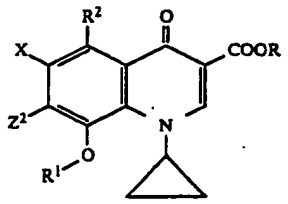


(VI)

wherein R^1, R^2, X and Z are same as above, by hydrolyzing according to usual method.

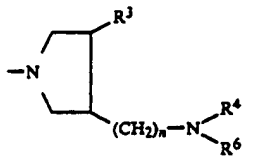
Such hydrolysis can be carried out easily at room temperature to boiling point of solvent in water, alcohols or mixed solutions thereof using alkalies such as sodium hydroxide and potassium hydroxide or acids such as hydrochloric acid and sulfuric acid.

Next, among the compounds represented by the general formula (I), compounds represented by a general formula (VII);

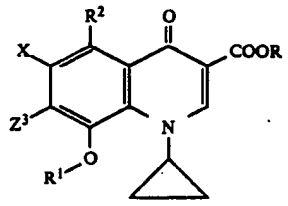


(VII)

wherein Z^2 indicates pyrrolidino group of the following formula,

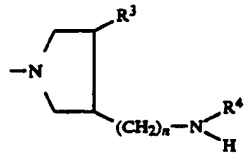


(here, R^6 indicates an acyl group or alkoxycarbonyl group, and n, R^3 and R^4 are same as above), and R, R^1, R^2 and X are same as above, can be converted to compounds represented by a general formula (VIII);



(VIII)

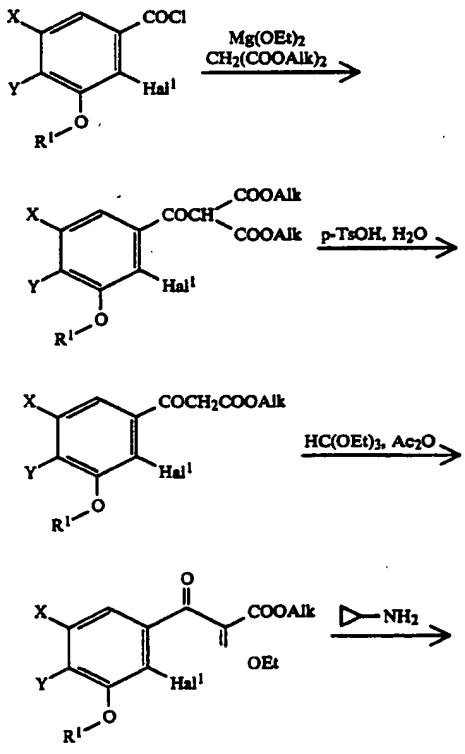
wherein Z^3 indicates pyrrolidino group of the following formula,



(here, R^3 and R^4 are same as above.), and R, R^1, R^2 and X are same as above, by submitting to deacylation.

Such reaction can be carried out easily by the methods well known usually such as hydrolysis with acid or alkali catalyst, catalytic reduction, etc.

The synthetic intermediates represented by the general formula (II) for the preparation of the compounds of the invention are also novel compounds and can be prepared through, for example, following route.



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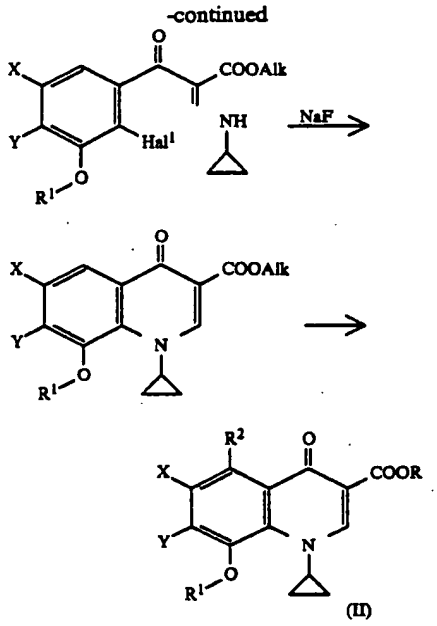
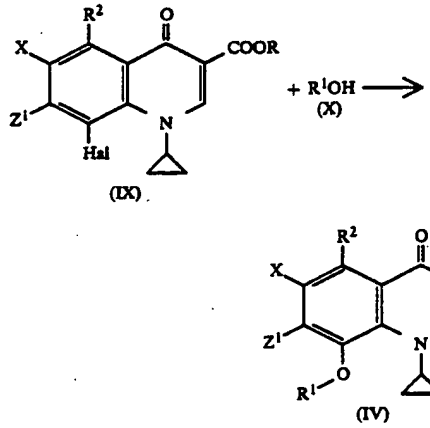


(wherein Hal^1 indicates a halogen atom, and Alk, R, R^1, R^2, X and Y are same as above.)

The compounds of the invention represented by the general formula (I) can also be prepared by allowing compounds represented by a general formula (IX) to act with alcohols represented by a general formula (X) as follows:



wherein Hal indicates a halogen atom, and R, R^1, R^2, X and Z^1 are same as above.

Such reaction is carried out without solvent or in the solvents such as alcohols, acetonitrile, DMSO, DMF, HMPA, dioxane, benzene, etc. in the presence of deacidifying agent, and it is desired to be carried out under anhydrous condition in order to suppress the side reactions. As the deacidifying agents, alkali fluoride, alkali metal alcoholate, alkali hydride, etc. can be used, but it is suitable to use alcohols represented by a general formula R^1OH as solvents, to allow these to act with alklai metals such as sodium, potassium, lithium, etc., and to submit to the reaction as they are.

In more detail, it is suitable to allow the compounds represented by the formula (IX) to react with at least

not less than equivalent moles of foregoing deacidifying agent and alcohols represented by the general formula R^1OH for 1 to 200 hours at room temperature to 200° C. in 1 to 50 times volume of foregoing solvents per volume of the compound (IX), and, when using low boiling point solvents, it is more advantageous to allow to react at high temperature in a sealed tube.

Next, the compounds represented by the formula (I) can be converted to the salts thereof according to usual method, if necessary. As the salts, for example, those with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, etc., those with organic acids such as methanesulfonic acid, lactic acid, oxalic acid, acetic acid, etc., or salts of sodium, potassium, magnesium, calcium, aluminum, cerium, chromium, cobalt, copper, iron, zinc, platinum, silver, etc. can be mentioned.

Furthermore, when the compounds of the invention are administered to human being or animals and plants, the shapes and the routes well known pharmaceutically up to this time are applied. They are used orally or parenterally through, for example, powders, tablets, capsules, ointments, injections, syrups, liquids, eye drops, suppositories, etc.

The following examples will further illustrate the invention without, however, limiting it thereto.

EXAMPLE 1

Synthesis of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), anhydrous piperazine (180 mg) and anhydrous dimethyl sulfoxide (DMSO; 3 ml) was stirred for 2.5 hours at 70° to 80° C. on an oil bath. The reacting mixture was concentrated under reduced pressure and cold water was added to the residue. The precipitate was collected by filtration and recrystallized from a mixed solution of dichloromethane-methanol (1:1) to give the title compound (40 mg) as pale yellow prisms, mp 187° C. (decompd.).

Analysis (%) for $C_{18}H_{20}FN_3O_4.2\ H_2O$; Calcd. (Found): C, 54.40 (53.96); H, 6.09 (5.99); N, 10.57 (10.34).

EXAMPLE 2

Synthesis of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), N-methylpiperazine (140 mg) and anhydrous DMSO (3 ml) was stirred for 5 hours at 70° to 95° C. on an oil bath. The reacting mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography eluting with chloroform-methanol-concentrated aqueous ammonia (20:6:1), the residue was recrystallized from methanol to give the title compound (50 mg) as colorless needles, mp 221°-222° C. (decompd.).

Analysis (%) for $C_{19}H_{22}FN_3O_4$; Calcd. (Found): C, 60.79 (60.82); H, 5.91 (5.90); N, 11.19 (11.24).

EXAMPLE 3

Synthesis of
1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), 2-methylpiperazine (140 mg) and anhydrous DMSO (3 ml) was stirred for 2 hours at 70° to 95° C. on an oil bath. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography eluting with chloroform-methanol-concentrated aqueous ammonia (20:6:1), the residue was recrystallized from methanol to give the title compound (50 mg) as white powdery crystals, mp 162° C.

Analysis (%) for $C_{19}H_{22}FN_3O_4.\frac{1}{2}\ H_2O$; Calcd. (Found): C, 59.37 (59.95); H, 6.03 (6.01); N, 10.93 (10.81).

EXAMPLE 4

Synthesis of
7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

To a suspension of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (2 g) in anhydrous acetonitrile were added 3-t-butoxycarbonylaminopyrrolidine (1.86 g) and 1,8-diazabicyclo[5,4,0]undec-7-en (DBU, 1.02 g) and then the mixture was refluxed for 3 hours. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in chloroform (50 ml). The resulting solution was washed with 10% aqueous citric acid solution (20 ml), and with saturated saline solution successively. The organic layer was dried over anhydrous sodium sulfate and then concentrated. The residue was dissolved in hot methanol (20 ml) and then cooled. The resulting crystals were collected by filtration to give 7-(3-t-butoxycarbonylamino-1-pyrrolidinyl)-1-cyclopropyl-1,4-dihydro-6-fluoro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (2.25 g) as yellowish white prisms, mp 224°-226° C. (decompd.).

Analysis (%) for $C_{23}H_{28}FN_3O_6.\frac{1}{2}\ H_2O$; Calcd. (Found): C, 59.28 (59.18); H, 6.22 (6.08); N, 9.02 (8.82).

To a suspension of these crystals (2.23 g) in methanol (16 ml) was added concentrated hydrochloric acid (16 ml) dropwise. After stirring for 3 hours at room temperature, the reaction mixture was cooled and neutralized with concentrated aqueous ammonia. The resulting precipitate was collected by filtration and washed with methanol and ether successively to give the title compound (1.52 g) as white powder, mp 217°-218° C.

Analysis (%) for $C_{18}H_{20}FN_3O_4.\frac{1}{2}\ H_2O$; Calcd. (Found): C, 58.37 (58.68); H, 5.71 (6.10); N, 11.35 (11.14).

EXAMPLE 5

Synthesis of
7-(cis-3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), cis-3-t-butoxycarbonylamino-4-methylpyrrolidine (150 mg), DBU (110 mg) and anhydrous acetonitrile (3 ml) was refluxed for 5 hours. After cooling, the resulting

precipitate was collected by filtration. This precipitate was added to the mixture of concentrated hydrochloric acid-methanol (1:1, 6 ml) and stirred for 1.5 hours at room temperature. The reaction mixture was neutralized by concentrated aqueous ammonia and allowed to stand in the refrigerator. The resulting crystals were collected by filtration and washed with cold water to give the title compound (90 mg) as colorless prisms, mp 185°–188 ° C. (decompd.).

Analysis (%) for $C_{19}H_{22}FN_3O_4.3/2\ H_2O$; Calcd. (Found): C, 56.71 (56.53); H, 6.26 (6.17); N, 10.44 (10.37).

EXAMPLE 6

Synthesis of 7-(trans-3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (0.40 g), trans-3-t-butoxycarbonylamino-4-methylpyrrolidine (0.41 g), DBU (0.21 g) and anhydrous acetonitrile (5 ml) was refluxed for 2.5 hours and then the reaction mixture was concentrated under reduced presure. The residue was dissolved in chloroform (40 ml) and washed with 10% aqueous citric acid solution (20 ml) and with saturated saline (20 ml) successively. The organic layer was dried over anhydrous sodium sulfate and then concetrated under reduced pressure. The residue was crystallized from ethanol to give 7-(trans-3-t-butoxycarbonylamino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-3-methoxy-4-oxo-3-quinolinecarboxylic acid. To a suspension of these crystals in methanol (5 ml) was added concentrated hydrochloric acid (5 ml) dropwise. After stirring for 1.5 hours at room temperature, the reaction mixture was neutralized with concentrated aqueous ammonia, the resulting crystals were collected by filtration and washed with water sufficiently to give the title compound (0.29 g) as colorless powder, mp 214°–215 ° C.

Analysis (%) for $C_{19}H_{22}FN_3O_4$; Calcd. (Found): C, 60.07 (60.41); H, 5.97 (5.80); N, 11.06 (11.05).

REFERENTIAL EXAMPLE 1

Synthesis of 3-methoxy-2,4,5-trifluorobenzoic acid

According to the method by Bardon et al. (Tetrahedron, 22, 2541 (1966)), 1,2,3,4-tetrafluorobenzene (50 g) was brominated and methoxylated to give 1-bromo-3-methoxy-2,4,5-trifluorobenzene (22.2 g) as colorless oil.

A mixture of the oily product (22 g), cuprous cyanide (10 g) and N-methyl-2-pyrrolidone (37 ml) in sealed tube was heated for 4.5 hours at 140° to 150° C. After cooling, a solution of ferric chloride hexahydrate (44 g) and concentrated hydrochloric acid (11 ml) in water (60 ml) was added to the reaction mixture and then stirred at 50° to 60° C. for 20 minutes. The reaction mixture was extracted with ether and the organic layer was washed with dilute aqueous hydrochloric acid, with water and with saturated saline solution successively, and dried over anhydrous sodium sulfate and then concentrated. The residue was purified by distillation under reduced pressure to give 3-methoxy-2,4,5-trifluorobenzonitrile (14.25 g) as colorless oil, bp 94° C./8 mmHg.

To oily product thus obtained (14.2 g) were added concentrated sulfuric acid (8.5 ml) and water (40 ml) and the mixture was stirred for 1 hour at 110° C. After cooling, the reaction mixture was poured into ice water (50 ml) and the resulting precipitate was collected by filtration, washed with water, and recrystallized from a solution of dichloromethane-n-hexane to give 3-methoxy-2,4,5-trifluorobenzamide (11.59 g) as white needle, mp 130°–133° C.

Then, to these crystals were added 18 N sulfuric acid (150 ml) and the mixture was heated for 3.5 hours at 100° C. After cooling, water (400 ml) was added to the mixture and the resulting crystals were recrystallized from n-hexane to give the title compound (9.61 g) as colorless needle, mp 98°–101° C.

Analysis (%) for $C_8H_5F_3O_3$; Calcd. (Found): C, 46.62 (46.68); H, 2.45 (2.48).

REFERENTIAL EXAMPLE 2

Synthesis of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

To 3-methoxy-2,4,5-trifluorobenzoic acid (9.4 g) was added thionyl chloride (50 ml), the mixture was refluxed for 3 hours and then concentrated. The residue was purified by distillation under reduced pressure to give 3-methoxy-2,4,5-trifluorobenzoyl chloride (8.86 g) as yellow oil, bp 108°–112° C./20 mmHg.

To magnesium ethoxide (5.9 g) was added diethyl malonate (7 g) in anhydrous toluene (35 ml) dropwise and the mixture was warmed for 2 hours at 50° to 60° C. and then cooled to −10° C. To the mixture was added a solution of the acid chloride (8.86 g) in anhydrous toluene (10 ml) dropwise over 15 minutes. After stirring for 1 hour at −5° to 0° C., ice water (30 ml) containing concentrated sulfuric acid (8 ml) was added to the mixture and the organic layer was separated. The organic layer was washed with saturated saline solution, dried over anhydrous sodium sulfate and then concentrated to give diethyl 3-methoxy-2,4,5-trifluorobenzoylmalonate (13.64 g) as brown oil.

To oily product, the malonate (13.55 g) were added water (20 ml) and p-toluenesulfonic acid (14 mg), and the mixture was refluxed for 9 hours. After cooling, the reaction mixture was extracted with dichloromethane and the organic layer was washed with 7% aqueous sodium bicarbonate solution and with saturated saline soluton succesively, dried over anhydrous sodium sulfate and then concentrated to give ethyl 3-methoxy-2,4,5-trifluorobenzoylacetate (10.29 g).

To the benzoyl acetate (9.79 g) were added acetic anhydride (9.6 g) and ethyl orthoformate (8.4 g), and the mixture was refluxed for 3 hours. After supplemented further acetic anhydride (3.2 g) and ethyl orthoformate (8.8 g), the mixture was refluxed for 8 hours, and then concentrated to give ethyl 2-(3-methoxy-2,4,5-trifluorobenzoyl)-3-ethoxyacrylate (9.73 g) as brown oil.

To a solution of the acrylate (9.73 g) in ethanol (20 ml) was added cyclopropylamine (2.0 g) dropwise under cooling. After stirring for 2 hours at room temperature, the reaction mixture was concentrated and the residue was purified by silica gel column chromatography eluting with n-hexane-ethyl acetate (5:1) to give ethyl 2-(3-methoxy-2,4,5-trifluorobenzoyl)-3-cyclopropylaminoacrylate (7.52 g) as yellowish white crystals, mp 56°–58° C.

Analysis (%) for $C_{16}H_{16}F_3NO_4$; Calcd. (Found): C, 55.98 (56.07); H, 4.70 (4.66); N, 4.08 (4.07).

The mixture of the aminoacrylate (6.68 g), sodium fluoride (1.31 g) and anhydrous dimethylformamide (26 ml) was refluxed for 5 hours. After cooling the reaction

mixture was poured into ice water (100 ml) and the resulting precipitate was collected by filtration, washed with water and recrystallized from ethyl acetate to give ethyl 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylate (4.53 g) as colorless needle, mp 178°–180° C.

Analysis (%) for $C_{16}H_{15}F_2NO_4$; Calcd. (Found): C, 59.44 (59.34); H, 4.68 (4.59); N, 4.33 (4.33).

To these crystals (4.5 g) was added a mixed solution of acetic acid (30 ml), concentrated sulfuric acid (4 ml) and water (22 ml), and the mixture was refluxed for 1 hour. After cooling, ice water (100 ml) was added and the resulting precipitate was collected by filtration, washed with water and then dried to give title compound (4 g) as colorless powder, mp 185°–186° C.

Analysis (%) for $C_{14}H_{11}F_2NO_4$; Calcd. (Found): C, 56.95 (56.68); H, 3.76 (3.70); N, 4.74 (4.74).

EXAMPLE 7

Synthesis of 7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), 3-aminomethylpyrrolidine (80 mg), DBU (110 mg) and anhydorous acetonitrile (3 ml) was refluxed for 2.5 hours. After cooling, the resulting precipitate was collected by filtration and recrystallized from a solution of dichloromethane-methanol (1:1) to give the title compound (90 mg) as white powdery crystals, mp 198°–200° C.

Analysis (%) for $C_{19}H_{22}FN_3O_4$; Calcd. (Found): C. 60.79 (60.39); H, 5.91 (5.87); N, 11.19 (11.07).

EXAMPLE 8

Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methylaminomethyl-1-pyrrolidinyl)-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), 3-methylaminomethylpyrrolidine (90 mg), DBU (110 mg) and anhydrous acetonitrile (3 ml) was refluxed for 75 minutes. After cooling, the resulting precipitate was collected by filtration and recrystallized from a solution of dichloromethane-methanol (1:1) to give the title compound (130 mg) as white powdery crystals, mp 226.5°–230° C.

Analysis (%) for $C_{20}H_{24}FN_3O_4 \cdot \frac{1}{2}\ H_2O$; Calcd. (Found): C, 60.29 (60.49); H, 6.32 (6.08); N, 10.54 (10.48).

EXAMPLE 9

Synthesis of 1-cyclopropyl-7-(3-ethylaminomethyl-1-pyrrolidinyl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A mixture of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (200 mg), 3-ethylaminomethylpyrrolidine (100 mg), DBU (110 mg) and anhydrous acetonitrile (3 ml) was refluxed for 6 hours. After cooling, the resulting precipitate was collected by filtration and recrystallized from methanol to give the title compound (120 mg) as colorless prisms, mp 217°–219° C.

Analysis (%) for $C_{21}H_{26}FN_3O_4 \cdot \frac{1}{2}\ H_2O$; Calcd. (Found): C, 60.71 (60.59); H, 6.63 (6.43); N, 10.11 (10.03).

REFERENTIAL EXAMPLE 3

Synthesis of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-5-nitro-4-oxo-3-quinolinecarboxylic acid

To a solution of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (490 mg) in concentrated sulfuric acid (5 ml) was added potassium nitrate (235 mg) below 5° C. under stirring portionwise. After stirring for 45 minutes, the reaction mixture was poured into ice water (25 ml) and the resulting precipitate was collected by filtration, washed with cold water sufficiently, recrystallized from a solution of dichloromethane-methanol (1:1) to give the title compound (392 mg) as yellow prisms, mp 215.5°–221° C. (decompd.).

Analysis (%) for $C_{14}H_{10}F_2N_2O_6$; Calcd. (Found): C, 49.42 (49.37); H, 2.96 (2.94); N, 8.23 (8.12).

REFERENTIAL EXAMPLE 4

Synthesis of 5-amino-1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

To a solution of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-5-nitro-4-oxo-3-quinolinecarboxylic acid (322 mg) in ethanol-DMF (4:1) was added 10% palladium-carbon (25 mg) and the mixture was stirred in hydrogen gas atomosphere for 6 hours at room temperature. The catalyst was filtered off and washed with a solution of chloroform-methanol-concentrated aqueous ammonia (10:10:3). The filtrate and washings were combined and concentrated. The residue was recrystallized from a solution of chloroform-methanol-concentrated aqueous ammonia (20:6:1) to give the title compound (183 mg) as yellow prisms, mp 291°–291.5° C. (decompd.).

Analysis (%) for $C_{14}H_{12}F_2N_2O_4$; Calcd. (Found): C, 54.20 (54.46); H, 3.90 (3.89); N, 9.03 (8.97).

EXAMPLE 10

Synthesis of 5-amino-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (72 mg), anhydrous piperazine (60 mg) and anhydrous DMSO (3 ml) was stirred for 2 hours at 70°to 80° C. and then concentrated under reduced pressure. A solution of the residue into aqueous ethanol acidified with concentrated hydrochloric acid below pH 1. The solution was allowed to stand in a refrigerator. The resulting precipitate was collected by filtration and washed with aqueous ethanol, then with ethanol to give the title compound (33 mg) as yellow flaky crystals, mp 271°–273° C. (decompd.).

Analysis (%) for $C_{18}H_{21}FN_4O_4.HCl.H_2O$; Calcd. (Found): C, 50.18 (50.28); H, 5.61 (5.48); N, 13.00 (12.97).

EXAMPLE 11

Synthesis of 5-amino-7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

A mixture of 5-amino-1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (90 mg), 3-t-butoxycarbonylaminopyrrolidine (115 mg), DBU (50 mg) and anhydrous acetonitrile (4 ml) was refluxed for 20 hours. After cooling, the resulting precipitate was collected by filtration and added to concentrated hydrochloric acid-methanol (1:1, 2 ml). The mixture was stirred for 10 minutes at room temperature, then neutralized with concentrated aqueous ammonia, and the precipitate was collected by filtration. A solution of the precipitate in cold water was acidified with concentrated hydrochloric acid below pH 1 and allowed to stand in a refrigerator. The resulting precipitate was collected by filtration and washed with cold diluted aqueous hydrochloric acid to give the title compound (35 mg) as yellow needles, mp 254°–257° C. (decompd.).

Analysis (%) for $C_{18}H_{21}FN_4O_4 \cdot 2\ HCl$; Calcd. (Found): C, 48.12 (48.16); H, 5.16 (5.53); N, 12.47 (12.52).

EXAMPLE 12

Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

To the solution of sodium methoxide prepared from sodium (0.2 g) and absolute ethanol (9 ml) was added 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (0.5 g) and the mixture in sealed tube was heated for 72.5 hours at 140° to 150° C. After cooling, the reaction mixture was concentrated, water (4 ml) was added to the residue, and the solution was adjusted to pH 7 with acetic acid. The insoluble materials were filtered off and the filtrate was allowed to stand in a refrigeretor. The resulting precipitate was collected by filtration and recrystallized from dichloromethane-methanol (2:1; 6 ml) to give the title compound (0.12 g) as colorless prisms, mp 185°–187.5° C. (decompd.).

Analysis (%) for $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2}\ H_2O$; Calcd. (Found): C, 58.37 (57.98); H, 5.71 (5.52); N, 11.35 (11.28).

EXAMPLE 13

Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

In a mixture of sodium formate (22 mg), 87% formic acid (0.3 ml) and 37% formalin (25 μl) and 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (60 mg) was stirred for 2 hours at 100° to 120° C. After cooling, water (1 ml) was added to the reaction mixture and then concentrated. To the residue was added water (0.5 ml), adjusted to pH 7 with 1 N aqueous sodium hydroxide solution and the solution was allowed to stand in a refrigerator. The resulting precipitate was collected by filtration and washed with water to give the title compound (33 mg) as colorless needles, mp 229°–232° C. (decompd.).

Analysis (%) for $C_{19}H_{22}FN_3O_4$; Calcd. (Found): C, 60.79 (60.80); H, 5.91 (5.90); N, 11.19 (11.15).

EXAMPLE 14

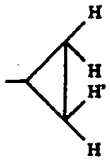
Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid

To a solution of sodium methoxide prepared from sodium (0.4 g) and absolute methanol (20 ml) was added 1-cyclopropyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (1.12 g), and, the mixture in sealed tube was stirred for 70.5 hours at 140° to 150° C. and then concentrated. The residue was dissolved in small amount of water, the resulting solution was adjusted to pH 7 with acetic acid and concentrated. The resulting residue was purified by silica gel column chromatography eluting with chloroform-methanol-concentrated aqueous ammonia (20:6:1) and recrystallized from methanol to give the title compound (0.33 g) as pale yellow prisms, mp 162° C.

Analysis (%) for $C_{19}H_{22}FN_3O_4 \cdot \frac{1}{2}\ H_2O$; Calcd. (Found): C, 59.37 (59.48); H, 6.03 (5.70); N, 10.93 (11.07).

H-NMR (δ in $CDCl_3$): 8.79 (1 H, s, 2-position), 7.85 (1 H, m, J=12.3 Hz, 5-position), 4.1–3.9 (1 H, m,

3.77 (3 H, s, OCH_3), 3.5–2.9 (7 H, m, piperazine), 1.3–1.0 (7 H, m,



CH_3)

EXAMPLE 15

Synthesis of 7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

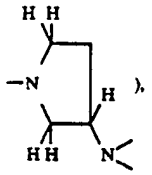
To a solution of sodium methoxide prepare from sodium (0.2 g) and absolute methanol (10 ml) was added 7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3quinolinecarboxylic acid (0.47 g) and the mixture in sealed tube was stirred for 49 hours at 140° to 150° C. and then concentrated. The residue was purified by silica gel column chromatography eluting with chloroform-methanol-concentrated aqueous ammonia (20:6:1) and recrystallized from a solution of dichloromethanemethanol (1:1) to give the title compound (6 mg) as pale yellow prisms, mp 207.5°–212° C.

Analysis (%) for $C_{18}H_{20}FN_3O_4 \cdot H_2O$; Calcd. (Found): C, 56.99 (57.19); H, 5.82 (5.38); N, 11.13 (10.86).

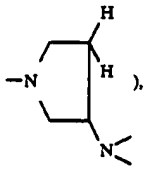
Mass analysis (m/e): 361 (M^+), 362 ($M^+ + 1$).

H-NMR (δ in D_2O, NaOD): 8.48 (1 H, s, 2-position), 7.62 (1 H, d, J=14.5 Hz, 5-position), 4.1–3.9 (1 H, m,

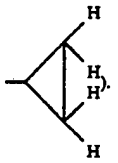
3.55 (3 H, s, OCH_3), 3.8–3.2 (5 H, m,



2.3–1.6 (2 H, m,



1.2–0.9 (4 H, m,



EXAMPLE 16

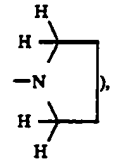
Synthesis of
7-(3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

To a solution of sodium methoxide prepare from sodium (50 mg) and absolute methanol (3 ml) was added 7-(3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (80 mg) and the mixture in sealed tube was stirred for 86 hours at 140° to 150° C. and then concentrated. Small amount of water was added to the residue, and the solution was adjusted pH 7 with acetic acid and concentrated. The resulting residue was purified by silica gel column chromatography eluting with chloroform-methanol-concentrated aqueous ammonia (20:6:1) and recrystallized from a solution of dichloromethane-methanol (1:1) to give the title compound (9 mg) as pale yellow prisms, mp 191.5°–193.5° C.

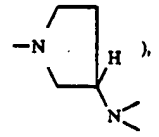
Analysis (%) for $C_{19}H_{22}FN_3O_4.7/5\ H_2O$; Calcd. (Found): C, 56.96 (57.10); H, 6.24 (5.98); N, 10.49 (10.42).

H-NMR (δ in D_2O, NaOD): 8.47 (1 H, s, 2-position), 7.57 (1 H, d, J=14.5 Hz, 5-position), 4.1–3.9 (1 H, m,

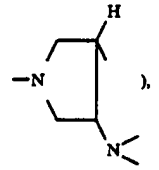
3.51 (3 H, s, OCH_3), 3.8–3.2 (4 H, m,



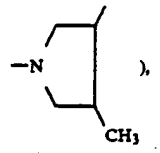
3.2–2.9 (1 H, q,



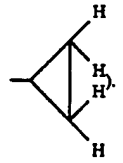
2.1–1.7 (1 H, m,



1.09 (3 H, d, J=6.59 Hz,



1.3–0.7 (4 H, m,



EXAMPLE 17

Synthesis of
7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid

To a solution of sodium methoxide prepare from sodium (0.2 g) and absolute methanol (9 ml) was added 7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (0.5 g) and the mixture in sealed tube was stirred for 86 hours at 140° to 150° C. and then concentrated. Small amount of water was added to the residue, and the

solution was adjusted pH 7 with acetic acid and then concentrated. The resulting residue was purified by silica gel column chromatography eluting with chloroform-methanol-concentrated aqueous ammonia (20:6:1) and recrystallized from methanol to give the title compound (40 mg) as pale yellow prisms, mp 225°–228.5° C. (decompd.).

Analysis (%) for $C_{19}H_{22}FN_3O_4 \cdot \frac{1}{2} H_2O$; Calcd. (Found): C, 58.91 (58.73); H, 6.07 (5.92); N, 10.85 (10.88).

EXAMPLE 18

Synthesis of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-ethoxy-4-oxo-7-(1-piperazinyl)3-quinolinecarboxylic acid

To a solution of sodium ethoxide prepare from sodium (0.75 g) and absolute ethanol (30 ml) was added 1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid (0.8 g) and the mixture in sealed tube was stirred for 52 hours at 140° to 150° C. and then concentrated. Water (60 ml) was added to the residue, and the solution was adjusted pH 7 with acetic acid and and extracted with chloroform. The chloroform layer was washed with saturated saline solution, dried over anhydrous sodium sulfate and then concentrated. The resulting residue was purified by silica gel column chromatography eluting with chloroform-methanol (2:1)→chloroform-methanol-concentrated aqueous ammonia (20:6:1→10:10:1) and recrystallized from ethanol to give the title compound (75 mg) as light brown prisms, mp 119°–122° C.

Analysis (%) for $C_{19}H_{22}FN_3O_4 \cdot \frac{1}{2} H_2O$; Calcd. (Found): C, 59.37 (59.60); H, 6.03 (6.04); N, 10.93 (10.85).

TEST EXAMPLE 1

Antibacterial spectra

The antibacterial test was carried out according to the method designated by Japan Society of Chemotherapy. The results are shown in Table 1.

TABLE 1

In vitro antibacterial activity

Organism (10^6 cells/ml)	Gram	MIC (μg/ml) Ex. 1	Ex. 2	Ex. 3	Ex. 4
Bacillus subtilis PCI 219	+	0.025	0.025	0.025	0.025
Staphylococcus aureus 209 P	+	0.10	0.10	0.10	0.05
S. aureus IID 670 (Terajima)	+	0.10	0.10	0.10	0.05
S. aureus Smith	+	0.10	0.10	0.10	0.05
S. epidermidis IID 866	+	0.10	0.10	0.10	0.10
Streptococcus pyogenes (S-8)	+	—	—	—	0.05
S. pyogenes IID 692	+	—	—	—	0.10
S. pneumoniae IID 552	+	—	—	—	0.10
E. faecalis IID 682	+	—	—	—	0.10
Escherichia coli NIHJ JC-2	−	≦0.0063	0.0125	≦0.0063	0.0125
E. coli ATCC 10536	−	0.025	0.025	0.0125	0.025
E. coli ML 4707	−	0.025	0.025	0.0125	0.025
Proteus vulgaris IFO 3167	−	0.0125	0.025	0.025	0.025
P. mirabilis IID 994	−	0.025	0.05	0.025	0.05
Morganella morganii IID 602	−	0.05	0.10	0.10	0.05
Klebsiella pneumoniae KY(GN)6445	−	0.025	0.05	0.025	0.05
K. pneumoniae 1-220S	−	0.05	0.10	0.05	0.05
Enterobacter cloacae IID 977	−	0.05	0.10	0.05	0.05
Citrobacter freundii IID 976	−	0.025	0.05	0.025	0.05
Serratia marcescens IID 618	−	0.05	0.10	0.10	0.05
Shigella sonnei IID 969	−	0.0125	0.025	0.0125	0.025
Salmonella enteritidis IID 604	−	0.05	0.10	0.05	0.05
Pseudomonas aeruginosa V-1	−	0.10	0.39	0.20	0.39
P. aeruginosa IFO 12689	−	0.78	1.56	1.56	0.39
P. aeruginosa IID 1210	−	0.39	1.56	1.56	0.39
P. cepacia GIFU 518	−	0.78	1.56	1.56	0.39
P. maltophilia GIFU 2491	−	0.39	0.20	0.20	0.10
Yersinia enterocolitica IID 981	−	0.05	0.10	0.05	0.05
Acinetobacter anitratus IID 876	−	0.10	0.10	0.10	0.05
Alcaligenes faecalis 0114002	−	0.20	0.39	0.39	0.39
Bacteroides fragilis GM 7000	−	0.78	0.39	0.39	0.20
B. fragilis 0558	−	0.39	0.20	0.39	0.10
B. fragilis 25285	−	0.39	0.39	0.39	0.10
B. distasonis 8503	−	1.56	0.39	0.78	0.78
B. thetaiotaomicron (0661)	−	1.56	1.56	0.78	0.20
B. vulgatus KYA 29327	−	0.78	0.39	0.78	0.39
Fusobacterium mortiferum 4249	−	0.39	0.78	0.78	0.20
F. necrophorum S-45	−	0.39	0.78	0.39	0.20
F. varium KYA 8501	−	3.13	6.25	6.25	1.56
Eubacterium lentum GAI 5242	+	0.20	0.20	0.20	0.10
Propionibacterium acens 11828	+	3.13	6.25	6.25	1.56
Peptococcus magnus KY 017	+	0.20	0.20	0.20	0.10
Clostridium difficile I-E	+	3.13	1.56	3.13	0.39
C. perfringens KYA 13123	+	0.39	0.39	0.39	0.20
C. ramosum	+	3.13	3.13	3.13	0.78
Peptostreptococcus anaerobius KYA 27337	+	0.39	0.78	0.39	0.20
Pst. micros UPI 5464-1	+	0.20	0.39	0.20	0.20
Veillonella parrula KYA 10790	−	0.20	0.39	0.20	0.20

Organism (10^6 cells/ml)	Gram	MIC (μg/ml) Ex. 5	Ex. 6	Ex. 7	Ex. 8

TABLE 1-continued

In vitro antibacterial activity					
Bacillus subtilis PCI 219	+	0.0125	0.0125	0.025	0.025
Staphylococcus aureus 209 P	+	0.025	0.025	0.025	0.05
S. aureus IID 670 (Terajima)	+	0.05	0.05	0.025	0.05
S. aureus Smith	+	0.05	0.05	0.05	0.05
S. epidermidis IID 866	+	0.10	0.10	0.05	0.05
Streptococcus pyogenes (S-8)	+	0.10	0.05	—	0.05
S. pyogenes IID 692	+	0.10	0.10	—	0.05
S. pneumoniae IID 552	+	0.10	0.10	—	0.05
E. faecalis IID 682	+	0.10	0.10	—	0.05
Escherichia coli NIHJ JC-2	−	0.0125	0.0125	0.025	0.025
E. coli ATCC 10536	−	0.0125	0.0125	0.05	0.05
E. coli ML 4707	−	0.025	0.0125	0.05	0.05
Proteus vulgaris IFO 3167	−	0.025	0.05	0.05	0.05
P. mirabilis IID 994	−	0.05	0.05	0.05	0.05
Morganella morganii IID 602	−	0.05	0.10	0.20	0.39
Klebsiella pneumoniae KY(GN)6445	−	0.025	0.05	0.05	0.05
K. pneumoniae 1-220S	−	0.05	0.05	0.10	0.10
Enterobacter cloacae IID 977	−	0.05	0.05	0.10	0.20
Citrobacter freundii IID 976	−	0.05	0.05	0.05	0.05
Serratia marcescens IID 618	−	0.05	0.05	0.20	0.20
Shigella sonnei IID 969	−	0.025	0.0125	0.05	0.05
Salmonella enteritidis IID 604	−	0.05	0.05	0.05	0.10
Pseudomonas aeruginosa V-1	−	0.78	0.78	0.20	0.78
P. aeruginosa IFO 12689	−	0.78	0.78	0.78	3.13
P. aeruginosa IID 1210	−	0.78	0.78	0.78	12.5
P. cepacia GIFU 518	−	0.78	0.39	0.78	1.56
P. maltophilia GIFU 2491	−	0.10	0.05	0.20	0.39
Yersinia enterocolitica IID 981	−	0.05	0.05	0.10	0.10
Acinetobacter anitratus IID 876	−	0.05	0.05	0.05	0.20
Alcaligenes faecalis 0114002	−	0.20	0.20	0.39	1.56
Bacteroides fragilis GM 7000	−	0.10	0.10	0.39	0.39
B. fragilis 0558	−	0.10	0.10	0.20	0.39
B. fragilis 25285	−	0.10	0.10	0.20	0.39
B. distasonis 8503	−	0.39	0.39	0.78	3.13
B. thetaiotaomicron (0661)	−	0.10	0.20	0.39	3.13
B. vulgatus KYA 29327	−	0.20	0.20	0.39	3.13
Fusobacterium mortiferum 4249	−	0.20	0.20	0.20	0.39
F. necrophorum S-45	−	0.20	0.20	0.20	0.39
F. varium KYA 8501	−	1.56	1.56	0.78	3.13
Eubacterium lentum GAI 5242	+	≦0.05	≦0.05	0.39	0.20
Propionibacterium acens 11828	+	1.56	3.13	0.39	0.78
Peptococcus magnus KY 017	+	0.10	≦0.05	0.05	≦0.05
Clostridium difficile I-E	+	0.39	0.78	0.39	—
C. perfringens KYA 13123	+	0.20	0.20	0.20	0.20
C. ramosum	+	0.78	0.78	0.78	0.39
Peptostreptococcus anaerobius KYA 27337	+	0.20	0.10	0.05	0.20
Pst. micros UPI 5464-1	+	0.20	0.20	0.10	0.39
Veillonella parvula KYA 10790	−	0.20	0.20	0.10	0.39

		MIC (μg/ml)			
Organism (10^6 cells/ml)	Gram	Ex. 9	Ex. 10	Ex. 11	Ex. 18
Bacillus subtilis DCI 219	+	0.0063	0.025	0.0125	≦0.05
Staphylococcus aureus 209 P	+	0.0125	0.05	0.025	0.20
S. aureus IID 670 (Terajima)	+	0.0125	0.10	0.05	0.39
S. aureus Smith	+	0.0125	0.10	0.025	0.39
S. epidermidis IID 866	+	0.025	—	—	0.39
Streptococcus pyogenes (S-8)	+	0.025	0.39	0.20	1.56
S. pyogenes IID 692	+	0.05	>0.78	0.39	3.13
S. pneumoniae IID 552	+	0.025	>0.78	0.20	0.78
E. faecalis IID 682	+	0.05	0.39	0.20	1.56
Escherichia coli NIHJ JC-2	−	0.0063	0.025	0.025	≦0.05
E. coli ATCC 10536	−	0.025	0.05	0.025	≦0.05
E. coli ML 4707	−	0.025	0.05	0.025	≦0.05
Proteus vulgaris IFO 3167	−	0.025	0.10	0.20	≦0.05
P. mirabilis IID 994	−	0.025	0.20	0.10	0.10
Morganella morganii IID 602	−	0.20	0.20	0.20	0.39
Klebsiella pneumoniae KY(GN)6445	−	0.05	0.05	0.05	≦0.05
K. pneumoniae 1-220S	−	0.10	0.20	0.20	0.20
Enterobacter cloacae IID 977	−	0.10	0.20	0.05	0.20
Citrobacter freundii IID 976	−	0.055	0.05	0.05	0.10
Serratia marcescens IID 618	−	0.10	0.20	0.20	0.20
Shigella sonnei IID 969	−	0.025	0.025	0.025	≦0.05
Salmonella enteritidis IID 604	−	0.05	0.20	0.10	0.10
Pseudomonas aeruginosa V-1	−	0.39	0.39	0.78	0.78
P. aeruginosa IFO 12689	−	1.56	1.56	1.56	3.13
P. aeruginosa IID 1210	−	6.25	1.56	1.56	6.25
P. cepacia GIFU 518	−	0.78	1.56	1.56	3.13
P. maltophilia GIFU 2491	−	0.20	0.20	0.20	0.39
Yersinia enterocolitica IID 981	−	0.10	0.20	0.10	0.20
Acinetobacter anitratus IID 876	−	0.05	0.10	0.05	0.10

TABLE 1-continued

	In vitro antibacterial activity				
Alcaligenes faecalis 0114002	–	0.78	0.78	0.78	0.78
Bacteroides fragilis GM 7000	–	0.10	3.13	1.56	3.13
B. fragilis 0558	–	0.10	3.13	1.56	12.5
B. fragilis 25285	–	0.10	3.13	1.56	3.13
B. distasonis 8503	–	0.78	6.25	12.5	12.5
B. thetaiotaomicron (0661)	–	0.78	6.25	1.56	12.5
B. vulgatus KYA 29327	–	0.39	0.39	0.78	12.5
Fusobacterium mortiferum 4249	–	0.20	1.56	3.13	3.13
F. necrophorum S-45	–	0.20	1.56	1.56	3.13
F. varium KYA 8501	–	1.56	50	25	25
Eubacterium lentum GAI 5242	+	0.10	0.78	0.39	1.56
Propionibacterium acens 11828	+	1.56	12.5	6.25	12.5
Peptococcus magnus KY 017	+	≦0.05	1.56	0.78	0.78
Clostridium difficile I-E	+	—	—	—	—
C. perfringens KYA 13123	+	≦0.05	3.13	0.78	1.56
C. ramosum	+	0.20	1.56	1.56	—
Peptostreptococcus anaerobius KYA 27337	+	≦0.05	1.56	0.78	3.13
Pst. micros UPI 5464-1	+	0.39	0.39	0.78	0.78
Veillonella parrula KYA 10790	+	0.39	0.39	0.78	0.78

Organism (10^6 cells/ml)	Gram	MIC (μg/ml) CPFX	MNZ
Bacillus subtilis PCI 219	+	0.05	—
Staphylococcus aureus 209 P	+	0.20	—
S. aureus IID 670 (Terajima)	+	0.20	—
S. aureus Smith	+	0.39	—
S. epidermidis IID 866	+	0.20	—
Streptococcus pyogenes (S-8)	+	0.39	—
S. pyogenes IID 692	+	0.78	—
S. pneumoniae IID 552	+	0.78	—
E. faecalis IID 682	+	0.78	—
Escherichia coli NIHJ JC-2	–	0.0063	—
E. coli ATCC 10536	–	0.0125	—
E. coli ML 4707	–	0.0125	—
Proteus vulgaris IFO 3167	–	0.0125	—
P. mirabilis IID 994	–	0.0125	—
Morganella morganii IID 602	–	0.025	—
Klebsiella pneumoniae KY(GN)6445	–	0.0125	—
K. pneumoniae 1-220S	–	0.025	—
Enterobacter cloacae IID 977	–	0.025	—
Citrobacter freundii IID 976	–	0.0063	—
Serratia marcescens IID 618	–	0.025	—
Shigella sonnei IID 969	–	0.0063	—
Salmonella enteritidis IID 604	–	0.025	—
Pseudomonas aeruginosa V-1	–	0.05	—
P. aeruginosa IFO 12689	–	0.20	—
P. aeruginosa IID 1210	–	0.78	—
P. cepacia GIFU 518	–	0.39	—
P. maltophilia GIFU 2491	–	0.39	—
Yersinia enterocolitica IID 981	–	0.025	—
Acinetobacter anitratus IID 876	–	0.10	—
Alcaligenes faecalis 0114002	–	0.39	—
Bacteroides fragilis GM 7000	–	6.25	0.78
B. fragilis 0558	–	3.13	0.78
B. fragilis 25285	–	3.13	0.78
B. distasonis 8503	–	6.25	0.39
B. thetaiotaomicron (0661)	–	>12.5	0.78
B. vulgatus KYA 29327	–	>12.5	0.39
Fusobacterium mortiferum 4249	–	1.56	0.20
F. necrophorum S-45	–	0.78	—
F. varium KYA 8501	–	>12.5	0.39
Eubacterium lentum GAI 5242	+	0.78	0.10
Propionibacterium acens 11828	+	12.5	0.78
Peptococcus magnus KY 017	+	0.39	0.78
Clostridium difficile I-E	+	12.5	0.20
C. perfringens KYA 13123	+	0.39	0.10
C. ramosum	+	12.5	0.39
Peptostreptococcus anaerobius KYA 27337	+	1.56	—
Pst. micros UPI 5464-1	+	0.20	0.78
Veillonella parrula KYA 10790	–	0.20	0.78

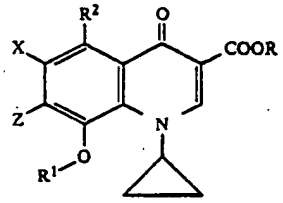
Contrast compounds

CPFX: Ciprofloxacin
MNZ: Metronidazole

The compounds of the invention was more excellent against gram-positive bacteria than ciprofloxacin known hitherto and exhibited high activity anaerobic bacteria equal to metronidazole being recommended by medical specialists.

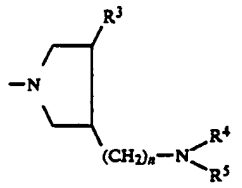
What is claimed is:

1. 8-Alkoxyquinolonecarboxylic acid derivatives represented by a general formula (I);



(I)

wherein R indicates a hydrogen atom or lower alkyl group, R^1 indicates a lower alkyl group, R^2 indicates a hydrogen atom X indicates a halogen atom, and Z indicates a halogen atom, piperazino group, N-methylpiperazino group, 3-methylpiperazino group, 3-hydroxypyrrolidino group, or pyrrolidino group of the following formula,



where, n is 0 or 1, R^3 indicates a lower alkylgroup, R^4 indicates a hydrogen atom, lower alkyl group, hydroxy-substituted lower alkyl group or halogenated lower alkyl group and R^5 indicates a hydrogen atom, lower alkyl group, acyl group or alkoxycarbonyl group, the hydrates or the pharmaceutically acceptable acid addition or alklai salts thereof.

2. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid.

3. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.

4. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid.

5. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 7-(cis-3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

6. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 7-(trans-3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

7. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 7-(3-amino-4-methyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

8. 8-Alkoxyquinolonecarboxylic acid derivative as claimed in claim 1, wherein said derivative is 1-cyclopropyl-6-fluoro-1,4-dihydro-8-ethoxy-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid.

* * * * *

Exhibit 4

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,980,470

DATED : DECEMBER 25, 1990

INVENTOR(S) : MASUZAWA KUNIYOSHI ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page item [30]:

In the Foreign Application Priority Data the second item number is incorrect, please delete "1-220149" and insert --61-220149--.

Signed and Sealed this

Eleventh Day of August, 1992

Attest:

DOUGLAS B. COMER

Attesting Officer

Acting Commissioner of Patents and Trademarks

[redacted]

Exhibit 5

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PAYOR NUMBER
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MAIER & NEUSTADT, P.C.

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& NEUSTADT, P.C.
CRYSTAL SQUARE FIVE, SUITE 400
1755 SOUTH JEFFERSON DAVIS HIGHWAY
ARLINGTON, VA 22202

DATE MAILED
04/05/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

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If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,980,470	183	930	----	07/003,822	12/25/90	01/16/87	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	1703-021-0

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PTOL 439 (rev 4 88)

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ARLINGTON VA 22202

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APR 21 1998
OBLON, SPIVAK, MCCLELLAND
MAIER & NEUSTADT, P.C.

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If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,980,470	184	2100	----	07/003,822	12/25/90	01/16/87	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	1703-021-0

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,980,470

DATED : DECEMBER 25, 1990

INVENTOR(S) : MASUZAWA KUNIYOSHI ET AL.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Foreign Application Priority Data the second item number is incorrect, please delete "1-220149" and insert --61-220149--.

MAILING ADDRESS OF SENDER:

OBLON, SPIVAK ET AL.
1755 Jefferson Davis Highway, 4F
Arlington, Virginia 22202
(703) 521-5940

PATENT NO. 4,980,470

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